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Severe acute respiratory syndrome coronavirus 2 infection in patients with prostate cancer: A critical review

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ABSTRACT

Real-world data suggest a possible interplay between androgen deprivation therapy (ADT) and susceptibility to and the severity of SARS-CoV-2 infection. As ADT is the backbone of prostate cancer treatment, various authors have evaluated different patient cohorts but the evidence provided is conflicting. The aim of this review is to assess the available publications concerning the role of ADT in preventing or reducing the severity of SARS-CoV-2 infection. After a literature search we identified four full papers, five letters, and four meeting abstracts, but these used different search methods and the quality of the evidence varied. They frequently had different endpoints, did not report the status of the prostate cancer patients and evaluated heterogeneous populations. The available data do not support the view that ADT protects against SARS-CoV-2 infection. Larger and more precise studies are warranted, considering variables that affect infection outcomes as these significantly influence the reliability of the findings.

1. Introduction

Coronavirus disease 2019 (COVID-19) has been a public health emergency since the World Health Organisation declared severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection a pandemic on 11 March 2020. More than 183 million cases of COVID-19 have so far been recorded (Coronavirus, 2021), although it is likely that the overall burden of the disease is underestimated as only a proportion of symptomatic patients and their contacts have been reported: one seroprevalence study has suggested that the estimated rate of SARS-CoV-2 exposure is 10-fold higher than the incidence of reported cases (Havers et al., 2020). Since the beginning of the pandemic, various factors have been associated with infection severity and mortality, including old age and the number of pre-existing co-morbidities such as diabetes, cardiopulmonary disease, and immune depression (Zhou et al., 2020a).

One major subject of debate concerns the prognosis of cancer patients who develop SARS-CoV-2 infection. A recent review showed that patients with tumours and SARS-CoV-2 infection have a high probability of mortality, with comparatively higher and lower mortality rates in presence of lung and breast cancer, respectively (Tagliamento et al., 2021).

The findings of a number of retrospective studies are unclear in terms of the oncological populations evaluated (active *vs* inactive disease, active treatment *vs* therapeutic window, and chemotherapy *vs* immunotherapy *vs* targeted therapy *vs* hormone therapy). One large retrospective study of 59,989 patients receiving anti-tumour treatment found that the infection rate was higher than in the general population during the same period (0.68 % *vs* 0.39 %; RR 1.42; 95 % CI 1.29–1.56) (Aschele et al., 2021). Chemotherapy seems to be the only anti-cancer treatment that has a negative impact on the lethality of the infection (Lievre et al., 2020; Yekeduz et al., 2020). One multi-centre study of 890 cancer patients with confirmed COVID-19 infection showed a worsening gradient of mortality from breast cancer to hematological malignancies, and found that male gender, an older age, and the number of co-morbidities identified clusters of patients with significantly worse mortality rates (Pinato et al., 2020). The sex discordance in COVID-19 outcomes led to the hypothesis that there may be an interplay between androgen-related cell machinery and COVID-19 and, consequently, that androgen deprivation therapy (ADT) may prevent the virus from penetrating cells (Wambier et al., 2020). As ADT is the backbone treatment for advanced prostate cancer (PC), the first report suggesting the potentially protective effect of ADT on the susceptibility to

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SARS-CoV-2 infection and the clinical outcomes of PC patients (Montopoli et al., 2020) prompted a wide-ranging debate in the scientific community, and led to the further hypothesis that inhibiting androgen receptor machinery may play a preventive and even a curative role.

A recent systematic review and meta-analysis, which explored the association between SARS-CoV-2 infection and disease severity among PC patients on ADT, selected six retrospective studies comparing ADT and no-ADT patients: the authors concluded against this association since there was a non-significant association between the risk of SARS-CoV-2 infection and COVID-19 severity in PC patients treated with ADT (Sari Motlagh et al., 2021).

However, severity and lethality of SARS-CoV-2 infection in PC patients could depend on not only ADT administration but also a number of factors (age, comorbidities, tumour stage and extension) which are usually not considered in the available reports on this topic. Thus, it is very difficult to draw definitive conclusions

The aim of this review was to examine the real-world evidence for and against such hypotheses, and clarify some of their debatable aspects.

2. Virology and the possible involvement of the androgen pathway

SARS-CoV-2 is an enveloped, positive-stranded RNA betacoronavirus (Lu et al., 2020), and the host receptor for its cell entry is angiotensin-converting enzyme 2 (ACE2) (Zhou et al., 2020b), which binds to the receptor-binding gene region of its spike protein. Cellular protease TMPRSS2 also seems to be important for SARS-CoV-2 cell entry because cleaving the S glycoprotein induces viral activation (Hoffmann et al., 2020). SARS-CoV-2 infection is transmitted through respiratory droplets that penetrate the upper respiratory tract (Wang et al., 2020), and TMPRSS2 is expressed in aero-digestive tract epithelial cells (Bertram et al., 2012). In experimental mouse models of SARS-CoV-2 infection, TMPRSS2-deficient mouse strains develop less severe infection, show reduced viral spread within the airway, and have less damaged respiratory cells (Iwata-Yoshikawa et al., 2019).

Given gender-related differences in the severity of SARS-CoV-2 infection, it may be hypothesised that males and females differentially express TMPRSS2 in lung tissues. However, the experimental evidence is conflicting: it has been observed that TMPRSS2 mRNA expression in normal human lung samples is higher in men than in women ($P = 0.029$) (Asselta et al., 2020), but other studies of human and murine lung tissues have found similar levels of TMPRSS2 gene expression in males and females (Baratchian et al., 2021; Stopsack et al., 2020).

Be that as it may, the transcription of the TMPRSS2 gene is regulated by androgenic ligands and androgen receptors (Lin et al., 1999), and ADT reduces the expression of TMPRSS2 (Mostaghel et al., 2007). It is also interesting to note that regulation of the androgen axis also seems to affect the expression of ACE2: the upstream region of ACE2 shows androgen receptor binding in mouse and human prostate cells (Deng et al., 2021), and androgens regulate ACE2 in subsets of lung epithelial cells (Qiao et al., 2020).

Androgen-driven immune modulation is another mechanism by means of which androgens could influence the clinical outcomes of SARS-CoV-2 infection. It is known that androgens have various immunosuppressive effects (Bhatia et al., 2014) that lead to sex-related differences in immune responses (Klein and Flanagan, 2016), and this may explain the gender-related disparity in the outcomes of SARS-CoV-2 infection. In line with this, ADT may restore the immune-system (Aragon-Ching et al., 2007) and may protect against SARS-CoV-2 infection by reducing susceptibility to and/or the severity of the disease.

Taken together, the evidence described above provides a strong rationale for postulating potential interplay between ADT for prostate cancer and the development of SARS-CoV-2 infection, and an equally strong rationale for using interference with the androgen axis as a therapeutic strategy.

3. Clinical outcomes of SARS-CoV-2 infection in PC patients receiving ADT: a literature review

As mentioned above, the first paper describing the potentially protective role of ADT against susceptibility to and the severity of SARS-CoV-2 infection (Montopoli et al., 2020) led to a wide-ranging debate. The authors of the paper matched the patients recorded in their regional COVID-19 archive with those listed in their regional tumour registry in order to identify cancer patients with and without infection. They also obtained data concerning the use of ADT from the Regional Medicines Technical Commission. Among the 9280 SARS-CoV-2 patients, 118 (1.3 %) had PC. Interestingly, more males developed more severe complications that required more hospitalisation (60 % *vs* 40 %), and males accounted for more deaths (62 % *vs* 40 %). However, the PC patients receiving ADT were at less risk of developing SARS-CoV-2 infection than those not receiving ADT (odds ratio 4.05; 95 % CI 1.55−10.59). Moreover, there was an even greater difference between the PC patients receiving ADT and the patients with any other type of cancer (OR 4.86; 95 % CI 1.88-12.56). On the basis of these findings, the authors postulated that ADT was associated with a reduced probability of developing SARS-CoV-2 infection, and less severe infection outcomes. However, as the reference regional tumour registry was only updated to 1 January 2016, it did not list the PC patients diagnosed in the intervening four years and, consequently, the rate of PC patients developing SARS-CoV-2 infection may have been over-estimated.

A search of the PubMed and Scopus databases and the proceedings of ASCO, ESMO, AUA, and EAU meetings from 1 January 2020 to 1 September 2021 identified 14 studies reporting the outcomes of PC patients with SARS-CoV-2 infection: five were published in the form of full papers (Caffo et al., 2020a; Di Lorenzo et al., 2020; Jimenez-Alcaide et al., 2021; Klein et al., 2021; Montopoli et al., 2020), and the others as letters (5) (Caffo et al., 2020b; Dalla Volta et al., 2020; Koskinen et al., 2020; Kwon et al., 2021; Patel et al., 2020) or meeting abstracts (4) (Duarte et al., 2021; Patel et al., 2021; Sbrana et al., 2020; Tucker et al., 2021). The results are summarised in Table 1.

The proportion of patients being treated with ADT at the time of SARS-CoV-2 infection (ADT+) was reported by nine studies and ranged from 0.07 % (Montopoli et al., 2020) to 7.05 % (Jimenez-Alcaide et al., 2021); none of the studies published after the first by Montopoli et al. confirmed a very low rate of infection. Only five studies compared the incidence of infection in ADT + and ADT- patients (Jimenez-Alcaide et al., 2021; Klein et al., 2021; Koskinen et al., 2020; Kwon et al., 2021; Montopoli et al., 2020), and all but one found no statistically significant different incidence between the two groups.

The severity of infection outcomes in ADT + patients was usually expressed in terms of mortality, which ranged from 5.3%–38.2% (Caffo et al., 2020a, b; Dalla Volta et al., 2020; Jimenez-Alcaide et al., 2021; Klein et al., 2021; Kwon et al., 2021; Tucker et al., 2021). Two studies reported a mortality rate of 0%, but they respectively evaluated only one and two ADT + patients with infection (Di Lorenzo et al., 2020; Sbrana et al., 2020). Two studies investigated infection severity in terms of mortality and intensive care unit (ICU) admissions and, in these cases, severe outcomes were recorded in respectively 16.6 % and 25 % of patients (Koskinen et al., 2020; Montopoli et al., 2020). Comparison of infection severity by ADT use did not reveal any statistically significant difference in mortality in most cases (Jimenez-Alcaide et al., 2021; Koskinen et al., 2020; Kwon et al., 2021; Montopoli et al., 2020; Patel et al., 2020, 2021); the only one that suggested ADT had a statistically significant favourable impact on mortality only evaluated the outcomes of hospitalised patients (Duarte et al., 2021).

The available data seem to indicate that ADT does not have a protective effect on SARS-CoV-2 infection outcomes.

Table 1
Summary of reports on prostate cancer patients with SARS−COV-2 infection.

Author (report type)	# PC pts ADT+ (%)	# PC pts ADT- (%)	ADT definition	PC status	Infection incidence	Infection severity (endpoint: death)	Conclusions	Comments
Montopoli (P) (Montopoli et al., 2020)	5273 (12.4 %)	37161 (87.6 %)	Not specified	Not specified	ADT+ 4/ 5273 (0.07%) ADT- 114/ 37161 (0.3%) OR 4.05 95% CI 1.55-10.59 p = 0.0043	** ADT+ 1/4 (25 %) ADT- 31/ 114 (27.2 %) OR 4.40 95%CI 0.76-25.50 P = 0.09	ADT seems to provide partial protection against SARS-CoV-2 infection	Tumour registry updated to 2016 No data from clinical records
Koskinen (L)(Koskinen et al., 2020)	134 (38 %)	218 (62 %)	orchiectomy, GnRH analogue, GnRH antagonist, antiandrogens, enzalutamide, abiraterone	Not specified	ADT+ 6/134 (4.5%) ADT- 11/218 (5.0%) OR 0.88 95% CI 0.32-2.44 p = 0.81	** ADT+ 1/6 (16.6%) ADT- 3/11 (27.3%) OR 0.53 95%CI 0.04-6.66 p = 0.63	No ADT-related difference in the incidence or severity of SARS-CoV-2 infection	Mixed population including patients with mCRPC
Kwon (L)(Kwon et al., 2021)	799 (15.3 %)	4412 (84.7 %)	GnRH analogue or antagonist	Not specified	ADT+ 18/ 799 (2.3%) ADT- 79/ 4412 (1.8 %) OR 1.30 95% CI 0.78-2.19 p = 0.31	ADT+ 1/19 (5.3 %) ADT- 7/78 (9.0 %) OR 0.56 95 %CI 0.07-4.88 p = 0.60	No ADT-related difference in the incidence or severity of SARS-CoV-2 infection	
Patel (L)(Patel et al., 2020)	22 (37.9 %)	36 (62.1 %)	GnRH analogue or antagonist and/or castrate testosterone levels within 6 months of COVID-19 diagnosis	24 % M1 76 % M0	NA	OR 0.37 95%CI 0.08-1.80 p = 0.220	ADT may limit severe complications of COVID-19	No data concerning effect of ADT on susceptibility to infection Death OR adjusted for age, cardiac disease, pulmonary disease
Dalla Volta (L)(Dalla Volta et al., 2020)	83 (100 %)		Not specified	mCSPC 52% mCRPC 48%	3/83 (3.6%)	1/3 (33 %)	Protective role of ADT not confirmed	Absence of ADT-group
Duarte (A)(Duarte et al., 2021)	48 (44 %)	61 (56 %)	Not specified	Not specified	NA	OR 0.28 95%CI 0.12-0.66 p = 0.0036	Active use of ADT was associated with a reduced risk of death	Only hospitalised pts
Di Lorenzo (P)(Di Lorenzo et al., 2020)	72 (100 %)		GnRH analogue or antagonist	CRPC 33% CSPC 67%	2/72 (2.8%)	0/2 (0 %)	Investigating ADT role during COVID-19 could be useful	Absence of ADT-group
Patel (A) (Patel et al., 2021)	148 (31.8%)	317 (68.2 %)	Castrate levels of testosterone	284 localised 162 biochemi-cally relapsed or metastatic	NA	HR 1.28 95%CI 0.79-2.08 p = 0.317	No protective effect of ADT against severe COVID-19	Absence of population without COVID
Caffo (L)(Caffo et al., 2020b)	1949 (100 %)		GnRH analogue or antagonist	Metastatic	36/1949 (1.8 %)	11/36 (30.5 %)	Higher incidence than in Montopoli's paper; greater lethality in patients aged >70 years than in the general population	Absence of ADT-group Homogeneous population Review of clinical records
Caffo (P)(Caffo et al., 2020a)	1433 (100 %)		GnRH analogue or antagonist	mCRPC	34/1433 (2.3 %)	13/34 (38.2 %)	Less protective effect of ADT in mCRPC	Absence of ADT-group Homogeneous population Review of clinical records
			Not specified	Not specified				

(continued on next page)

Table 1 (*continued*)

Author (report type)	# PC pts ADT+ (%)	# PC pts ADT- (%)	ADT definition	PC status	Infection incidence	Infection severity (endpoint: death)	Conclusions	Comments
Klein (P)(Klein et al., 2021)	304 (17.1 %)	1475 (82.9 %)			ADT+ 17/304 (5.6 %) ADT- 85/1475 (5.8 %)	ADT+ 6/17 (35.3 %) ADT- 13/85 (15.3 %) OR 0.9 OR 2.9 95% CI 0.54-1.61	ADT did not protect against COVID infection	No data concerning PC stage
95% CI 0.86-9.81	p = 0.8							
Tucker (A)(Tucker et al., 2021)	198 (22.8 %) *107*(37 %)*	670 (77.2 %) *182*(63 %)*	Not specified	Not specified	NA	ADT+ 24/107 (22.4 %) ADT- 30/182 (16.5 %) AOR 1.25 *** 95%CI 0.59-2.65	No differences in COVID outcomes by ADT administration after propensity matching	Propensity analysis of COVID outcomes by additional PC treatments No data on PC stage
Sbrana (A)(Sbrana et al., 2020)	132 (100 %)		GnRH analogue with or without an antiandrogen	Not reported	1/132 (0.7 %)	0/1 (0 %)	Low incidence and severity	Absence of ADT-group
Jiménez-Alcaide (P) (Jimenez-Alcaide et al., 2021)	11 (18 %)	50 (82 %)	Not specified	27.3 % M1 72.7 % M0	ADT+ 11/156 (7.05 %) ADT- 114/1193 (4.2 %)	ADT+ 3/11 (27.3 %) ADT- 17/50 (34.0 %) RR, 0.67; 95 %CI 0.26–1.74	The use of ADT did not prevent the risk of severe COVID-19.	Death RR adjusted for age and comorbidities

A = abstract; ADT = androgen deprivation therapy; AOR = adjusted odds ratio; CRPC = castration-resistant prostate cancer; CSPC = castration-sensitive prostate cancer; GnRh = gonadotropin-releasing hormone; HR = hazard ratio; L = letter; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; NA = not available; OR = odds ratio; P = full paper; PC = prostate cancer; RR = risk ratio.

* Patients included in the propensity analysis in italics.

** Endpoint: death or need for intensive care.

*** 30-day mortality (data from poster available on line).

4. Critical factors affecting the outcomes of ADT + PC patients with SARS-CoV-2 infection

The comparability and interpretation of the available studies are methodologically limited by differences in patient selection and the fact that they did not explore a number of critical clinical and demographic factors that should be considered when assessing the interplay between ADT and SARS-CoV-2 infection outcomes.

First of all, most of the studies evaluated PC patients identified from hospital records (Caffo et al., 2020a, b; Dalla Volta et al., 2020; Di Lorenzo et al., 2020; Jimenez-Alcaide et al., 2021; Koskinen et al., 2020; Patel et al., 2020; Sbrana et al., 2020): this has the advantage of allowing the full availability of clinical information concerning disease stage and PC treatments, but excludes patients who are not regularly followed up in a hospital setting and screened for SARS-CoV-2 infection. In other words, a significant proportion of PC patients with or without COVID-19 (generally not receiving ADT) may be missed, and this can bias the study results. Duarte et al. selected their PC patients from a registry of patients with COVID-19 in public health system hospitals (Duarte et al., 2021), an approach that is clearly limited by the selection of patients with complicated disease. A more efficient approach started with COVID registries and then matched the screened patients with hospital records [20; 22; 25; 32]: this has the advantage of allowing infection susceptibility to be determined by comparing COVID + and COVID- subjects, but may be limited by the incompleteness of the clinical dataset and the inability to capture non-hospitalised PC patients. The data collected by the COVID-19 and Cancer Consortium (CCC19) were used to compare the outcomes of ADT + and ADT- PC patients (Tucker et al., 2021), but the voluntary nature of case collection around the world could affect the applicability of the study results to the more general context of unselected patients.

It may be more reasonable to adopt the approach used by Montopoli et al. Montopoli et al. (2020), who matched the records of their regional tumour registry with the records of the regional COVID registry. However, the tumour registry did not cover the previous four years of tumour diagnoses and the clinical data concerning ADT use should have been confirmed by clinical record screening.

In addition to these methodological issues, the available studies did not evaluate a number of clinical variables that may affect infection outcomes and are related to the characteristics of the patients and their oncological disease. First of all, patient-related variables that are known to have prognostic value in terms of the severity of the infection include an advanced age (>70 and, particularly, >80 years) and the cumulative number co-morbidities. Very few of the studies considered such variables in their analyses, but Koskinen et al. reported that there was no statistically significant difference in terms of the age (using a cut-off age of 65 years) or selected co-morbidities of their ADT + and ADT- patients (Koskinen et al., 2020); Kwon et al. considered age and co-morbidities in their multivariate analysis (Kwon et al., 2021); and Patel et al. adjusted the effect of ADT use on infection outcomes for age (not specified), cardiac disease, and pulmonary disease. However, as the risk of poor infection outcomes is higher in older subjects and is related to the cumulative number of co-morbidities, it is surprising that the authors considered a cut-off age of 65 years (and not older) and only evaluated individual co-morbidities rather than their cumulative number. Interestingly, Jiménez-Alcaide et al. evaluated the protective role of ADT by adjusting the analysis for age, Charlson Comorbidity Index, hypertension, and obesity: they failed to confirm this role for worse clinical evolution of infection or death (Jimenez-Alcaide et al., 2021).

Other factors relating to the characteristics of PC should also be

considered when evaluating SARS-CoV-2 infection outcomes.

4.1. The duration of ADT exposure

None of the reports described this, but it is clear that the impact of ADT on infection outcomes in a patient who has received ADT for a few weeks is very different from that in a patient who has been treated for several years. Furthermore, the duration of ADT exposure also affects the patients' general health as it induces changes in body composition and lipid profiles, and decreases insulin sensitivity (Faris and Smith, 2010). This not only increases the risk of osteoporosis, but also the risk of diabetes and obesity, both of which are additional risk factors for poor SARS-CoV-2 infection outcomes. It has been demonstrated that men receiving long-term ADT are insulin resistant and hyperglycemic (Basaria et al., 2006), and develop significant gains in body fat mass and losses in lean mass (Smith et al., 2002).

4.2. Prostate cancer status

The health of a patient receiving ADT for a biochemical recurrence is clearly different from that of a patient receiving ADT for metastatic PC. Patients who experience a biochemical relapse do not have clinically evident metastases, and their health status is due to the presence or absence of concomitant diseases, whereas the health of a significant proportion of patients with metastases is jeopardised by definition. Moreover, patients with metastatic castration-resistant PC (mCRPC) usually receive long-lasting ADT, which increases the risk of metabolic syndrome, and the use of additional treatments can lead to many side effects that increase patient frailty.

None of the reports distinguished the patients undergoing ADT on the basis of their cancer status, although one study of mCRPC patients found a relationship between the number of mCRPC treatment lines and infection outcomes, which suggests that patients with a longer history of active PC and more delivered treatments may have worse outcomes than those with a shorter history and less treatment exposure (Caffo et al., 2020a). Moreover, the mortality observed in this study suggests that, if ADT can protect against the complications of SARS-CoV-2 infection, it only does so in the early phase of PC. However, the results of the study of Jiménez-Alcaide et al. did not seem to confirm this possibility: although most of the patients (72 %) in this series did not present metastatic spread, the protective role of ADT was not supported (Jimenez-Alcaide et al., 2021).

4.3. Additional cancer treatments

As said above, ADT is administered with other agents to patients with more advanced PC, and the addition of chemotherapy, androgen-receptor signalling inhibitors (ARSI), or radiopharmaceuticals represents the standard of care in those with mCRPC. It has been widely debated whether chemotherapy-related immune depression is an additional risk factor for poor SARS-CoV-2 infection outcomes, but this is not supported by epidemiological data (Pinato et al., 2020), and the only study that specifically focused on a small cohort of mCRPC patients did not find that chemotherapy-treated patients had poorer infection outcomes than the patients receiving ARSI (Caffo et al., 2020a).

Tucker et al. evaluated SARS-CoV-2 infection outcomes in 138 patients who received another agent in addition to ADT (Tucker et al., 2021). Interestingly, the highest mortality rate was observed in the patients receiving chemotherapy, who also had the lowest hospitalisation rate, whereas the patients treated with enzalutamide had the highest rate of uncomplicated infections and the lowest mortality rate.

A further issue is the use of steroids, which are frequently administered to control symptoms or as per label concomitant medication in the case of treatment with chemotherapy or abiraterone. Consequently, a significant proportion of patients with advanced PC treated with ADT also receive long-term steroid treatment. It has been observed that corticosteroids are associated with severe infection outcomes among patients with inflammatory bowel disease, although no cause/effect relationship has yet been proven (Brenner et al., 2020). Any patient who regularly takes oral steroids should be considered at higher risk of developing infections and complications due to SARS-CoV-2 (Kaiser et al., 2020). This is mainly related to the immunosuppressive effects of a long-term steroid administration, and has led experts to warn against the use of abiraterone acetate and recommend alternative approved strategies (Ribal et al., 2020). There are no conclusive data concerning the effect of steroid exposure on infection outcomes, but steroid administration was considered in the multivariate analysis of the poster of Tucker et al. and did not seem to have any effect on infection severity (Tucker et al., 2021): however, the duration of the exposure was not specified.

5. Conclusions

A number of studies have reported the outcomes of patients receiving ADT for PC who developed SARS-CoV-2 infection, but their conflicting findings concerning the protective role of ADT in terms of infection susceptibility and severity can be explained by considering their methodological differences and, mainly, their failure to capture information that critically contributes to infection outcomes, such as age, comorbidities, and factors related to the patients' PC history.

The overall feeling is that ADT does not provide protection against SARS−COV-2 infection, except perhaps in the early phases of PC, and that mCRPC patients who develop SARS−COV-2 infection have a poorer prognosis than patients in earlier stages of the disease. Nevertheless, larger prospective population studies are warranted in order to clarify the relationship between ADT and the severity of SARS−COV-2 infection in patients with PC.

Declaration of Competing Interest

OC received honoraria from Astellas, Astra Zeneca, Bayer, Janssen, Pfizer, was advisor for Astellas, Janssen, MSD, was speaker for Astellas

The other authors have no disclosure to make.

References

Aragon-Ching, J.B., Williams, K.M., Gulley, J.L., 2007. Impact of androgen-deprivation therapy on the immune system: implications for combination therapy of prostate cancer. Front Biosci 12, 4957–4971.

Aschele, C., Negru, M.E., Pastorino, A., et al., 2021. Incidence of SARS-CoV-2 Infection Among Patients Undergoing Active Antitumor Treatment in Italy. JAMA Oncol. 7 (2), 304–306.

Asselta, R., Paraboschi, E.M., Mantovani, A., Duga, S., 2020. ACE2 and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. Aging (Albany NY) 12 (11), 10087–10098.

Baratchian, M., McManus, J.M., Berk, M.P., et al., 2021. Androgen regulation of pulmonary AR, TMPRSS2 and ACE2 with implications for sex-discordant COVID-19 outcomes. Sci. Rep. 11 (1), 11130.

Basaria, S., Muller, D.C., Carducci, M.A., Egan, J., Dobs, A.S., 2006. Hyperglycemia and insulin resistance in men with prostate carcinoma who receive androgen-deprivation therapy. Cancer 106 (3), 581–588.

Bertram, S., Heurich, A., Lavender, H., et al., 2012. Influenza and SARS-coronavirus activating proteases TMPRSS2 and HAT are expressed at multiple sites in human respiratory and gastrointestinal tracts. PLoS One 7 (4), e35876.

Bhatia, A., Sekhon, H.K., Kaur, G., 2014. Sex hormones and immune dimorphism. Sci. World J. 2014, 159150.

Brenner, E.J., Ungaro, R.C., Gearry, R.B., et al., 2020. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. Gastroenterology 159 (2), 481–491 e3.

Caffo, O., Gasparro, D., Di Lorenzo, G., et al., 2020a. Incidence and outcomes of severe acute respiratory syndrome coronavirus 2 infection in patients with metastatic castration-resistant prostate cancer. Eur. J. Cancer 140, 140–146.

Caffo, O., Zagonel, V., Baldessari, C., et al., 2020b. On the relationship between androgen-deprivation therapy for prostate cancer and risk of infection by SARS-CoV-2. Ann. Oncol. 31 (10), 1415–1416.

Coronavirus (COVID-19) disease pandemic- Statistics & Facts. https://www.statista.com/page/covid-19-coronavirus (accessed on 4 July 2021).

Dalla Volta, A., Valcamonico, F., Zamboni, S., et al., 2020. Is androgen deprivation therapy protective against SARS-CoV-2 infection and related complications in prostate cancer patients? Minerva Urol. Nefrol. 72 (6), 778–779.
Deng, Q., Rasool, R.U., Russell, R.M., Natesan, R., Asangani, I.A., 2021. Targeting androgen regulation of TMPRSS2 and ACE2 as a therapeutic strategy to combat COVID-19. iScience 24 (3), 102254.
Di Lorenzo, G., Buonerba, L., Ingenito, C., et al., 2020. Clinical characteristics of metastatic prostate Cancer patients infected with COVID-19 in South Italy. Oncology 98 (10), 743–747.
Duarte, M.B.O., Leal, F., Argenton, J.L.P., Carvalheira, J.B.C., 2021. Impact of androgen deprivation therapy on mortality of prostate cancer patients with COVID-19: a propensity score-based analysis. J. Clin. Oncol. 39 (15_suppl), 5067.
Faris, J., Smith, M., 2010. Metabolic consequences of androgen deprivation therapy for prostate Cancer. Curr. Opin. Endocrinol. Diabetes Obes. 17 (3), 7.
Havers, F.P., Reed, C., Lim, T., et al., 2020. Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020. JAMA Intern. Med. 180 (12), 1576–1586, 2020.
Hoffmann, M., Kleine-Weber, H., Schroeder, S., et al., 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181 (2), 271–280 e8.
Iwata-Yoshikawa, N., Okamura, T., Shimizu, Y., et al., 2019. TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. J. Virol. 93 (6), e01815–18.
Jimenez-Alcaide, E., Garcia-Fuentes, C., Hernandez, V., et al., 2021. Influence of androgen deprivation therapy on the severity of COVID-19 in prostate cancer patients. Prostate. Ahead of print.
Kaiser, U.B., Mirmira, R.G., Stewart, P.M., 2020. Our response to COVID-19 as endocrinologists and diabetologists. J. Clin. Endocrinol. Metab. 105 (5) dgaa148.
Klein, S.L., Flanagan, K.L., 2016. Sex differences in immune responses. Nat. Rev. Immunol. 16 (10), 626–638.
Klein, E.A., Li, J., Milinovich, A., et al., 2021. Androgen deprivation therapy in men with prostate Cancer Does not affect risk of infection with SARS-CoV-2. J. Urol. 205 (2), 441–443.
Koskinen, M., Carpen, O., Honkanen, V., et al., 2020. Androgen deprivation and SARS-CoV-2 in men with prostate cancer. Ann. Oncol. 31 (10), 1417–1418.
Kwon, D.H., Vashisht, R., Borno, H.T., et al., 2021. Androgen-deprivation therapy and SARS-CoV-2 in men with prostate cancer: findings from the University of California health System registry. Ann. Oncol. 32 (5), 678–679.
Lievre, A., Turpin, A., Ray-Coquard, I., et al., 2020. Risk factors for Coronavirus Disease 2019 (COVID-19) severity and mortality among solid cancer patients and impact of the disease on anticancer treatment: a French nationwide cohort study (GCO-002 CACOVID-19). Eur. J. Cancer 141, 62–81.
Lin, B., Ferguson, C., White, J.T., et al., 1999. Prostate-localized and androgen-regulated expression of the membrane-bound serine protease TMPRSS2. Cancer Res. 59 (17), 4180–4184.
Lu, R., Zhao, X., Li, J., et al., 2020. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395 (10224), 565–574.
Montopoli, M., Zumerle, S., Vettor, R., et al., 2020. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (n=4532). Ann. Oncol. 31 (8), 1040–1045.
Mostaghel, E.A., Page, S.T., Lin, D.W., et al., 2007. Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. Cancer Res. 67 (10), 5033–5041.
Patel, V.G., Zhong, X., Liaw, B., et al., 2020. Does androgen deprivation therapy protect against severe complications from COVID-19? Ann. Oncol. 31 (10), 1419–1420.
Patel, V.G., Zhong, X., Shah, N.J., et al., 2021. The role of androgen deprivation therapy on the clinical course of COVID-19 infection in men with prostate cancer. J. Clin. Oncol. 39 (6_suppl), 41.
Pinato, D.J., Zambelli, A., Aguilar-Company, J., et al., 2020. Clinical portrait of the SARS-CoV-2 epidemic in European cancer patients. Cancer Discov. 10 (10), 1465–1474.
Qiao, Y., Wang, X.M., Mannan, R., et al., 2020. Targeting transcriptional regulation of SARS-CoV-2 entry factors ACE2 and TMPRSS2. Proc. Natl. Acad. Sci. U. S. A. 118 (1) e2021450118.
Ribal, M.J., Cornford, P., Briganti, A., et al., 2020. European association of urology guidelines office rapid reaction group: an organisation-wide collaborative effort to adapt the european association of urology guidelines recommendations to the coronavirus disease 2019 era. Eur. Urol. 78 (1), 21–28.
Sari Motlagh, R., Abufaraj, M., Karakiewicz, P.I., et al., 2021. Association between SARS-CoV-2 infection and disease severity among prostate cancer patients on androgen deprivation therapy: a systematic review and meta-analysis. World J. Urol. Ahead of print.
Sbrana, A., Paolieri, F., Bloise, F., et al., 2020. SARS-CoV-2 infection in prostate cancer patients: data from a high-incidence area in Italy. Ann. Oncol. 31 (Suppl 4), S934.
Smith, M.R., Finkelstein, J.S., McGovern, F.J., et al., 2002. Changes in body composition during androgen deprivation therapy for prostate cancer. J. Clin. Endocrinol. Metab. 87 (2), 599–603.
Stopsack, K.H., Mucci, L.A., Antonarakis, E.S., Nelson, P.S., Kantoff, P.W., 2020. TMPRSS2 and COVID-19: Serendipity or Opportunity for Intervention? Cancer Discov. 10 (6), 779–782.
Tagliamento, M., Agostinetto, E., Bruzzone, M., et al., 2021. Mortality in adult patients with solid or hematological malignancies and SARS-CoV-2 infection with a specific focus on lung and breast cancers: a systematic review and meta-analysis. Crit. Rev. Oncol. Hematol. 163, 103365.
Tucker, M.D., Schmidt, A.L., Hsu, C.-Y., et al., 2021. Severe-COVID-19 and mortality among patients (pts) with prostate cancer (PCa) receiving androgen deprivation therapy (ADT). J. Clin. Oncol. 39 (6_suppl), 39-39.
Wambier, C., Goren, A., Ossimetha, A., Nau, G., Qureshi, A., 2020. Androgen-driven COVID-19 pandemic theory. Res. Gate Publ.
Wang, D., Hu, B., Hu, C., et al., 2020. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 323 (11), 1061–1069.
Yekeduz, E., Utkan, G., Urun, Y., 2020. A systematic review and meta-analysis: the effect of active cancer treatment on severity of COVID-19. Eur. J. Cancer 141, 92–104.
Zhou, F., Yu, T., Du, R., et al., 2020a. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395 (10229), 1054–1062.
Zhou, P., Yang, X.L., Wang, X.G., et al., 2020b. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579 (7798), 270–273.

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