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Pharmacotherapeutic approach toward urological medications and vaccination during COVID-19: a narrative review

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***Abstract*:** One year after the prevalence of the novel coronavirus pandemic, some aspects of the physiopathology, treatment and progression of coronavirus 2019 disease (COVID-19) have remained unknown. Since no comprehensive study on the use of urological medications in patients with COVID-19 has been carried out, this narrative review aimed to focus on clinically important issues about the treatment of COVID-19 and urologic medications regarding efficacy, modifications, side effects and interactions in different urologic diseases. In this review, we provide information about the pharmacotherapeutic approach toward urologic medications in patients with COVID-19 infection. This study provides an overview of medications in benign prostatic hyperplasia, prostate cancer, impotence and sexual dysfunction, urolithiasis, kidney transplantation and hypertension as the most frequent diseases in which the patients are on long-term medications. Also, the effect of urologic drugs on the efficacy of vaccination is briefly discussed.

Keywords: COVID-19, drug interaction, major urological diseases

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Introduction

One year after the outbreak of the novel coronavirus 2019 disease (COVID-19), according to the World Health Organization (WHO) COVID 19 report, 205,338,159 confirmed cases have been identified worldwide, and 4,333,094 deaths have been recorded up to 13 August 2021.[1] Unfortunately, due to the progressive nature of SARS-CoV-2, and the absence of a definite treatment, healthcare systems around the world are under pressure in both providing the budget and resolving the shortage of human resources to tackle this pandemic. Also, due to the numerous mutations of the virus and the slow rate of vaccination in the world, the possibility of reduced effectiveness of the existing drugs and vaccines on new subtypes of COVID-19 exists; hence, it seems that COVID-19 is still one of the problems of the world health organization that must be dealt with using the experiences of the past years.[2]

It is essential that the physicians and other members of the healthcare systems be fully aware of all aspects of the suggestive medications in the management of COVID-19 to provide the optimized and safest treatment with minimal side effects and drug–drug interactions, especially in patients with poly-pharmacy status. Urology field is no exception to this rule, and in some cases such as benign prostatic hyperplasia (BPH), prostate cancer (PC), urolithiasis and kidney transplantation, the patients, especially the geriatric population, have been using multiple medications for many years.[3] Therefore, in this study, we aimed to review various aspects of pharmacotherapeutic approaches in terms of efficacy and safety for patients with common urological comorbidities that may interfere with COVID-19 and also evaluate possible efficacy of urologic medications in the COVID-19 management.

Benign Prostatic Hyperplasia (BPH)

BPH is one of the most common diseases in men aged above 45 years. This condition presents in

many forms including irritable and obstructive lower urinary tract symptoms (LUTS), urinary incontinence and urinary retention.[4] Up to 50% of the males over the age of 50, and up to 80% of those over the age of 80 experience LUTS due to BPH. The first step of treatment is medical management including Alpha-blockers, 5-alpha reductase inhibitors, phosphodiesterase inhibitors (PDE) and anti-muscarinic agents.[5]

It has been shown that androgens, such as testosterone, have crucial roles in prostate gland growth and function; therefore, castrated patients with BPH experience a considerable decrease in the prostate size and alleviation of LUTS.[6] Conversion of testosterone to a more potent androgen called dihydrotestosterone (DHT) occurs by 5-α reductase enzyme. High levels of DHT have been found to have a vital role in the pathophysiology of BPH; thus, agents such as Finasteride and Dutasteride which inhibit 5-α reductase enzyme are key options proposed for medical treatment of BPH.[7] Some studies have suggested that androgens are associated with exacerbation of COVID-19 symptoms.[8] A preliminary observational study, conducted in Spain showed that men with androgenic alopecia (AGA) were at higher risk of hospitalization for COVID-19 complications compared to the controls.[9] Studies have suggested that SARS-CoV-2 needs the transmembrane protease serine 2 (TMPRSS2) to modify the viral spike protein for entering the type-II pneumocystis cell.[10] TMPRSS2 gene promoter in humans is located in Region 5 of the promoter which is an androgen-response element. Blocking androgen leads to reduction of the expression of TMPRSS2.[11] In this regard, some studies suggest that the use of 5-α reductase inhibitors, such as dutasteride or finasteride, can be effective in relieving the symptoms and preventing the severe phase of COVID-19.[12] Cadegiani *et al.*[13] found that using dutasteride can dramatically improve remission of COVID-19 symptoms such as fatigue, as well as the loss of taste and smell. It has also been shown that patients with COVID-19 who have taken anti-androgenic medications such as dutasteride and spironolactone are less likely to be admitted in the intensive care unit (ICU) than the control age-matched group. However, Adamowicz *et al.*[14] have presented a hypothesis about susceptibility of patients taking 5-α reductase inhibitors to developing coronavirus infection and more severe presentation and impairment in the regeneration of the epithelium in the lungs through augmentation of the androgen levels. Therefore, these controversies regarding 5-α reductase inhibitors in patients with BPH are necessary to be considered.

Alpha-1 blockers are the first line of medical treatment in patients with BPH. The mechanism of these drugs is relaxation of the bladder neck and prostatic smooth muscle cells which result in improvement of BPH-related symptoms. Some short-acting selective α-1 blockers such as Prazosin have been used for decades; however, due to their bothersome side effects such as orthostatic hypotension, these types of medication have been recently less commonly prescribed by urologists. On the other hand, uroselective alpha-blockers which have higher affinity to α1d and α1a receptors such as tamsulosin and naftopidil are now the preferred choice in the treatment of BPH-related symptoms because of fewer side effects.[15–17]

Cytokine storm syndrome (CSS), in which an excessive amount of cytokines such as interleukin (IL)-6, IL-8, and tumor necrosis factor alpha (TNF-α) leads to acute lung injury and acute respiratory distress syndrome (ARDS), is associated with a surge in catecholamines theoretically. Catecholamines lead to cytokine release through α1-adrenergic receptor signaling pathway in the immune cells during the acute phase of COVID-19 infection. Furthermore, in some studies, the potential effects of prazosin in treating CSS have been discussed.[18,19]

Some clinical trials at multiple institutions have investigated the potential effect of prazosin in preventing CSS.[19] Moreover, another study suggested that tamsulosin was a preferred alpha-blocker in preventing ARDS progression in patients with COVID-19 who had experienced CSS.[20,21] According to these data, we suggest that alpha-blockers should be used in the corona crisis period although further studies are suggested. There are no potential drug–drug interactions (DDIs) between alpha-blockers or 5-alpha-reductase inhibitors with anti-COVID-19 drugs such as remdesivir, favipiravir, hydroxychloroquine and lopinavir/ritonavir (Table 1).

PDE inhibitors have a comparable effect with alpha-blockers in alleviation of LUTS in patients with BPH. Also, the combination of alpha-blockers and PDE inhibitors improves International Prostate Symptom Score (IPSS).[5] The safety and interaction of PDE inhibitors during COVID-19 crisis will be discussed in the next part.

Table 1. Drug–drug interactions and pharmacotherapy consideration regarding anti-COVID-19 and urological drugs.

Medication classes	Drug anti-COVID interactions	Considerations
5-alpha-reductase inhibitors	No potential DDIs reported so far	It is supposed that 5-alpha-reductase inhibitors have a protective role against severity of COVID-19
PDE inhibitors	Should avoid concomitant use with lopinavir/ritonavir If concomitant use is necessary, use tadalafil up to 20 mg daily	Taking tadalafil once a day theoretically improves the tissue vascularization and prevents fibrosis
SSRIs and TCAs	Lopinavir/ritonavir inhibits CYPs 3A4 which metabolizes SSRI, resulting in increased plasma concentration	Fluvoxamine and clomipramine are suggested as adjuvant therapy against COVID-19 due to their positive effects in the CRS.
NSAIDs	No potential DDIs reported so far	The use of NSAIDS may exacerbate some of the complications caused by COVID-19 such as thrombosis and kidney injury, so risk–benefit assessment should be done before prescriptions. Although some studies suggested that the use of ibuprofen should be avoided in patients with COVID-19 due to the deterioration of the respiratory status of these patients; it seems that ibuprofen up-regulates the ACE2, an entrance receptor for the coronavirus SARS-CoV-2. However, the FDA and European Medicines Agency (EMA) have stated that they have not reached a convincing evidence in this regard
Opioids	Due to the potential effects of methadone on QT prolongation, patients with COVID-19 who receive hydroxychloroquine or lopinavir/ritonavir should be under consideration to be monitored for QTc prolongation	It is recommended that buprenorphine should be used as the first choice, and then tramadol and oxycodone are recommended as second options in the pain management among COVID-19 patients
Imunosuppressants	Taking lopinavir/ritonavir can significantly increase the serum concentration of tacrolimus and cyclosporin. Concomitant use of hydroxychloroquine and cyclosporine increases the serum concentrations of cyclosporine	It is suggested that the anti-metabolites should be temporarily discontinued and calcineurin inhibitors should be continued with the minimum plasma level in non-severe patients. It is also recommended that in the severe cases of COVID-19, all immunosuppressants should be discontinued and replaced with corticosteroids
ACEIs and ARBs	No potential DDIs reported, so far	Neither treatment with an ACEI nor an ARB was associated with a greater likelihood of SARS-CoV-2 infection. It is suggested that in patients taking ACEI and/or ARBs there is no need to alter the dose in the course of COVID-19 pandemic
Antibiotics	In patients taking hydroxychloroquine, lopinavir/ritonavir, prescription of fluoroquinolones or azithromycin should be more cautiously done due to probability of QTc prolongation	The nephrotoxic side effects should be considered in concurrent use of aminoglycosides and remdesivir
HRT	Enzalutamide is a CYP3A4 inducer and can reduce lopinavir/ritonavir concentration	It seems safe to continue ADT treatment in people with prostate cancer during COVID-19 period
Alpha-blockers	No potential DDIs reported, so far	Some studies reported promising effects of alpha-blockers in the management of CRS among COVID-19 patients.

ACEIs: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; COVID-19: coronavirus 2019 diseases; CRS: cytokine release syndrome; CYP3A4: cytochrome P450 3A4; DDIs: drug-drug interactions; EMA: European Medicines Agency; HRT: hormone replacement therapy; NSAIDs: non-steroidal anti-inflammatory drugs; PDE: phosphodiesterase; TCAs: tricyclic antidepressants; SSRIs: selective serotonin reuptake inhibitors.

Impotence and sexual dysfunctions

Impotence along with decreased libido and erectile dysfunction are classified as male sexual dysfunction.[22] Psychotherapy, evaluation and treatment of chronic and underlying diseases with pharmacological therapy are the bases of management of these conditions.[23] One class of the medications used in the management of erectile dysfunction is PDE inhibitors, which include sildenafil and tadalafil. These medications inhibit the conversion of cyclic guanosine monophosphate (GMP) to its inactive form, 5'-GMP, by inhibiting the enzyme PDE type-5 inhibitor, thus increasing the nitric oxide (NO) levels, followed by vasodilation. In addition, this treatment is being used for pulmonary arterial hypertension (PAH) based on the same mechanism. During the COVID-19 pandemic, the use of these medications is under consideration. Studies have shown that these medications, by inhibiting NO-cGMP-PDE-5 axis, may counteract the Ang-II-mediated downregulation of the angiotensin-II receptor type-1 (AT-1), which causes a reduction in infiltration, pro-inflammatory cytokines and alveolar hemorrhage-necrosis.[24,25] Therefore, it seems that the use of these drugs can play a preventive role in the development of high-altitude pulmonary edema (HAPE) and subsequent ARDS in patients with COVID-19.[26] In this regard, since tadalafil is more selective against PDE5 than PDE6, some studies recommend, as a hypothesis, that taking tdalafil once a day theoretically improves the tissue vascularization and prevents fibrosis.[24] Also, one clinical trial (NCT04304313) has been conducted to find out the effects of sildenafil on controlling pulmonary symptoms among COVID-19 patients;[27] however, the results have not been published yet.

It should be considered that COVID-19 patients who use lopinavir/ritonavir, as part of their treatment regimen, should avoid concomitant use of sildenafil due to the increase in the level of sildenafil.[28] If it is necessary to prescribe PDE inhibitors such as in the PAH condition, at the same time with lopinavir/ritonavir, tadalafil is the best choice in case it is not taken with a higher dose than 20 mg daily in the first week.[29] It should be mentioned that PDE inhibitors are a part of medical management of BPH that might be prescribed for a longtime. As these patients are old, a urologist must pay special attention to monitoring those who take this kind of medicine.

Selective serotonin reuptake inhibitors (SSRIs), like sertraline, are used to treat premature ejaculation in some cases.[30] Some studies have stated that SSRIs can significantly decrease the level of pro-inflammatory cytokines, such as IL-6, TNF-α and CCL-2 and prevent the severe phase of COVID-19.[31,32] A recent *in vitro* study has also shown the antiviral effects of fluoxetine on SARS-CoV-2.[33] The results of a clinical trial also indicated that COVID-19 patients who had used fluvoxamine experienced less clinical deterioration than the control group, possibly due to its potent agonist effects on the σ-1-receptor (S1R).[34] The S1R, an endoplasmic reticulum chaperone protein, has many cellular functions, such as reducing damages after inflammatory response during sepsis and regulating the cytokine production.[35] On the contrary, clomipramine, one of the tricyclic antidepressants, which inhibits noradrenaline and serotonin uptake has been proven to have anti-inflammatory properties in many studies (human studies, *in vitro* and *in vivo* studies).[36,37] Studies also suggest that this medication can be one of the therapeutic candidates in patients with COVID-19.[38,39] SSRI and clomipramine users should consider drug interaction for the administration of lopinavir/ritonavir because it inhibits CYP 3A4 which metabolizes SSRIs and clomipramine, resulting in increased plasma concentration of these agents.[40]

Urolithiasis

Urinary tract and kidney stones are one of the main complaints that draw the patients to the urology clinic. Dietary regimens and medical management of renal stones play a crucial part in decreasing the recurrence of urolithiasis. According to the type of stones, the prescribed drugs are different. However, for patients with urinary stones for whom operation is non-emergent, conservative management for 3 months and re-evaluation thereafter are advised. In emergency cases, percutaneous nephrostomy tube insertion is the preferred temporary method, and when operation is indicated laparoscopy should be performed with caution. In patients in whom surgery is not indicated, lifestyle and dietary modifications are highly advised.[41]

Thiazides, xanthine oxidase inhibitors like allopurinol, sulfhydryl compounds such as D-Penicillamine or tiopronin (α-mercaptopropionylglycine), captopril and acetohydroxamic acid are the commonly used drugs in calcium, uric acid, cysteine and infectious calculi, respectively.[42] Among these medications, special attention should be paid to the use of

thiazides by patients due to their interaction with hydroxychloroquine or lopinavir/ritonavir and probable QT prolongation. In addition to non-pharmacological methods used to manage the condition, pharmacological interventions such as analgesia are frequently used for pain management in these patients. In the meantime, non-steroidal anti-inflammatory drugs (NSAIDs) are always one of the first choices in pain management which should be prescribed with more care during COVID-19 pandemic. As a matter of fact, some studies suggested that the use of ibuprofen should be avoided in patients with COVID-19 due to the deterioration of the respiratory status of these patients.[43,44] Their evidence focused on ibuprofen which up-regulates the angiotensin-converting enzyme 2 (ACE II), an entrance receptor for the coronavirus SARS-CoV-2.[45] However, the US Food and Drugs Administration (FDA) and European Medicines Agency (EMA) have stated that they have not found convincing evidence in this regard.[46] Also, it has been suggested that naproxen and indomethacin may also be effective against SARS-CoV-2 due to their proven antiviral effects,[47] but further research is required. On the contrary, caution should be exercised when prescribing NSAIDS for patients with COVID-19 because severe forms of COVID-19 can increase the risk of thrombosis and multiple organ failure; moreover, selective or non-selective NSAIDs increase the risk of venous thromboembolism by two or more times, too. Furthermore, NSAIDs can cause vasoconstriction by decreasing the vasodilator prostacyclin and increase blood pressure by sodium and water retention. Due to NSAID consumption, cyclooxygenase (COX) inhibition can potentially lead to the negative effects of angiotensin II on the kidney and may increase the risk of acute renal failure.[48] As a result, the use of NASIDs may exacerbate some of the complications caused by COVID-19. However, it is not yet clear whether patients who are using NASIDs are at higher risk for COVID-19 complications or not. Therefore, more care should be taken in prescribing these drugs during the COVID-19 pandemic.

Opioids are used to control moderate to severe cancer and non-cancer pain. Although long-term use of opioids for chronic non-malignant pain is controversial, in some cases, if the patients do not tolerate the use of NSAIDs to control their pain, opioids must be considered.[49] It is also recommended that opioids should not be used for more than 7 days for controlling acute pain.[50] Lethargy, nausea and gastrointestinal symptoms that are associated with COVID-19 infection could be worsened by prescribing opioids, like the case with medications used for neuropathic pain like gabapentin or pregabalin.[51] In case of opioid-tolerant patients, it is recommended that the minimum dose of opioids should be used to prevent opioid withdrawal syndrome. Also, it is suggested that opioids that have the least-negative effects on the immune system, including buprenorphine, should be used as the first choice and then tramadol and oxycodone as the second options.[52] Due to the potential effects of methadone on QT prolongation, patients with COVID-19 who receive hydroxychloroquine or lopinavir/ritonavir should be under consideration to be monitored for QTc prolongation. To avoid the exacerbation of this complication, it is better to use oxycodone in these conditions.[53]

Kidney transplantation

A group of patients with clinical importance during the pandemic period are those with solid organ transplantation. Due to the suppressed immune system, these patients are at higher risk of progressive forms of COVID-19.[54] The management of COVID-19 in transplant patients is challenging because a balance is needed between optimal immunosuppression to maintain the organ function, while preventing further suppression of the immune system to prevent the progression of COVID-19. On the contrary, the use of some recommended COVID-19 medications has potential and serious drug interactions with immunosuppressive agents, so management of transplanted patients affected by COVID-19 has special subtleties. So far, several guidelines have been published regarding the management of kidney transplant patients with COVID-19.[55,56] As previously mentioned, the management of immunosuppressant medications in this group of patients has not yet been well explained, but most studies have recommended that anti-metabolites should be temporarily discontinued, and calcineurin inhibitors should be continued with the minimum plasma level.[57] On the contrary, some studies have not recommended the use of mammalian target of rapamycin (mTOR) inhibitors due to the mTOR inhibitor-associated pneumonitis which can deteriorate the respiratory system status.[58] It is also recommended that in the severe cases of COVID-19, all immunosuppressant medications should be discontinued and replaced with corticosteroids, but the dose and duration of corticosteroid consumption are not yet clear.[57]

As mentioned before, caution should be exercised about serious drug–drug interactions between immunosuppressive drugs with some of the antivirals used in the treatment of COVID-19. For example, taking lopinavir/ritonavir can significantly increase the serum concentration of tacrolimus, so the daily dose of tacrolimus should be reduced to one-twentieth to one-fiftieth.[59] On the contrary, reducing the dose of cyclosporine is also necessary in the concomitant use of hydroxychloroquine.[60]

Renovascular hypertension

According to the published articles, it seems that hypertension is considered as one of the most common comorbidities among COVID-19 patients.[61,62] Renovascular hypertension (RVH) accounts for 1%–2% of hypertension causes, and up to 6.8% of the population aged more than 65 years old and 5.8% of young adults with hypertension suffered from these vascular lesions. Atherosclerotic renal artery stenosis (ARAS) and fibromuscular dysplasias (FMD) are the leading causes of RVH. The medical treatment of RVH is mostly based on renin–angiotensin aldosterone system blockade by consumption of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.[63] Although it is unclear whether uncontrolled blood pressure is a risk factor for affliction with COVID-19 or not, it has been identified that effective control of blood pressure is of particular importance. One of the controversial issues is starting or continuing renin–angiotensin system blockers in patients with COVID-19. There are concerns that the use of these medications can worsen the course of the disease, as SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE2) on the cell membrane for entry into the target cells. Although human studies on this fact are few, there is some experimental evidence indicating that renin–angiotensin system blockers up-regulate ACE2 in animal models.[64,65] Indeed, there is an alternative hypothesis that down-regulation of ACE2 in the cells infected with SARS-CoV-2 may result in angiotensin II–induced injury.[66,67] This is because ACE2 is the key enzyme involved in degradation of angiotensin II, the cleavage of which is also thought to produce other cytoprotective angiotensin peptides.[68] Consequently, rather than increasing the severity of COVID-19, renin–angiotensin system blockers might reduce it, and there is some experimental support for this hypothesis. Based on these findings, in a meta-analysis conducted on the safety of these drugs, it was concluded that neither treatment with an ACE inhibitor nor an angiotensin II receptor blocker (ARB) was associated with a greater likelihood of SARS-CoV-2 infection; also, the risk of ICU admission was not higher in patients treated with a renin–angiotensin system blocker, and this was true for likelihood of ventilation as well. Similarly, the case-fatality rate was not higher among patients treated with a renin–angiotensin system blocker.[69] As a result, it is suggested that in patients taking Angiotensin-converting enzyme inhibitors (ACEI) and/or ARBs, there is no need to alter the dose during COVID-19 pandemic.[70]

Urogenital infections

Using antibiotics is essential in some urological conditions, such as pyelonephritis, urethritis, prostatitis and sexually transmitted diseases. Cephalosporins, fluoroquinolones, sulfonamides and aminoglycosides are different antibiotic classes which are used more broadly in the urology field. These antibiotic classes are safe in patients infected with COVID-19 without any reported caution in this regard. It is noteworthy that in patients taking hydroxychloroquine and lopinavir/ritonavir, fluoroquinolones or azithromycin should be more cautiously prescribed due to the probability of QTc prolongation, while the nephrotoxic side effects should be kept in mind in concurrent use of aminoglycosides and remdesivir.[71,72]

Prostate Cancer(PC) and hormone replacement therapy

Some studies conducted since the onset of COVID-19 have shown that the incidence and mortality rate were higher in men than women. A meta-analysis of 39 observational studies has reported an increased proportion of men (57.4%; 8518/14,844) who required hospitalization due to COVID-19 infection compared with women.[73,74] Many hypotheses have been put forward to justify this fact, including the higher rate of smoking in men than in women and the higher prevalence of comorbidities such as diabetes and high blood pressure in men. Besides, one of the considerable hypotheses is that testosterone facilitates the entry of SARS-CoV-2 into the lung cells. As previously mentioned, SARS-CoV-2 requires the activity of the enzyme TMPRSS2 to enter the cell, which has been observed in cell studies. The transcription of

TMPRSS2 is promoted by androgens, so androgen receptor activity is essential for TMPRSS2 expression.[75,76]

For this reason, some attribute the higher prevalence and mortality of COVID-19 in men to the negative role of testosterone. However, there is some other evidence that the positive aspects of androgens should also be considered in the recovery of patients with COVID-19. As has been well explained so far, cytokine release syndrome has been suggested as the main etiology of severe cases of COVID-19 and mortality, which is generally mediated by IL-6. The results of epidemiological data have shown that COVID-19 affects the older age group disproportionately. It is also noteworthy that IL-6 concentrations are higher in the elderly, which is partly attributed to low testosterone levels.[77,78] In a crossover study of 27 men with symptomatic androgen deficiency, testosterone supplementation reduced the levels of pro-inflammatory tumor necrosis factor alpha (TNF-α), IL-1ß and IL-6 and increased the concentration of the anti-inflammatory cytokine, IL-10.[79] Testosterone is also documented to protect murine models from severe influenza by attenuating the pro-inflammatory cytokine response in the lung tissue.[80]

Therefore, it seems that in terms of the positive or negative effect of testosterone on the clinical outcomes of the patients with COVID-19, we should wait for future studies.[81] However, only a retrospective study of the clinical outcome of testosterone use in men has shown that testosterone replacement therapy (TRT) is not associated with a worse clinical outcome in men diagnosed with COVID-19.[82]

PC is the second most detected cancer and the fifth leading cause of cancer-based mortality in men.[15] Anti-androgens are the frequently used treatment in patients with PC in both forms of monotherapy, or in combination with LHRH analogues. It is estimated that about 50% of patients with PC are candidates of androgen deprivation therapy.[83] LHRH analogues, LHRH antagonists, nonsteroidal antiandrogens, and steroidal antiandrogens are the mainstay of this kind of treatment. Montopoli *et al.*[73] in a study of PC patients treated with androgen-deprivation therapies (ADTs), concluded that PC patients treated with ADT had a significantly lower risk of developing COVID-19 (OR 4.05). Therefore, it seems safe to continue ADT treatment in people with PC during the COVID period. It should be noted that in patients with PC taking enzalutamide, when co-administered with lopinavir/ritonavir in patients with COVID-19, care should be taken not to reduce the plasma concentration of lopinavir/ritonavir since this drug is a CYP3A4 inducer.[82]

Intravesical BCG for bladder cancer

BCG (bacillus calmette-guerin) vaccine was first discovered by a French scientist in 1921 against tuberculosis.[84] Further research showed that BCG has positive effects against human leukemia.[85] Moreover, intralesional injection of BCG can be used in the treatment of human melanoma.[86] Furthermore, BCG can be utilized as an immunotherapeutic agent in the treatment of non-muscle invasive bladder cancer (NMIBC).[87]

With the worldwide dispersion of COVID-19, some studies suggested that this vaccine might be effective in the treatment of COVID-19.[88] The recommended mechanism of action in this matter is based on the molecular similarity between BCG antigens and respiratory viral antigens which results in more efficient activation of memory B- and T-cells against SARS-CoV-2 in BCG-vaccinated patients. Other studies have suggested an antigen-independent pathway of bystander B- and T-cells' activation that plays an important role in heterologous immunity. Finally, studies have suggested that BCG vaccination can lead to long-term activation of the innate immune cells, and thus, the trained immune system. Such mechanisms are thought to be effective in the enhancement of the immune system against COVID-19.[89–91]

Some evidence has shown that in regions without a policy of universal BCG vaccination in Italy and the United States of America, higher mortality is seen among COVID-19 patients compared to regions with long-standing universal BCG vaccination in Japan and the Republic of Korea.[92] However, it is now evident that multiple risk factors and their complex interactions are responsible for COVID-19 morbidity and mortality; thus, the lower mortality in Japan and the Republic of Korea cannot be attributed to BCG vaccination alone. Some clinical trials are being conducted on BCG vaccination and COVID-19, the results of which have not been published yet.[93]

Vaccination

Vaccination is the most promising solution to end the COVID-19 pandemic. Currently, more than 50 vaccines are in their clinical trial phases and some vaccines have been approved by WHO for use in the prevention of COVID-19.[94] Although the distribution is not homogeneous and the rate of vaccination is not the same around the globe, the studies conducted in the developed countries show that vaccination can significantly decrease the severe form of COVID-19 and the mortality due to this disease.[95]

Although the efficacy and immunogenicity of vaccines do not seem to be different between non-cancerous urologic patients and the normal population, some concerns exist regarding the efficacy and immunogenicity of COVID-19 vaccines in immunocompromised patients like the ones who are under chemotherapy. Since these patients have been excluded from the studies, there is a lack of comprehensive data about the efficacy and immunogenicity of COVID-19 vaccines in this patient population. The data in this regard is limited to some small studies.[96,97]

Monin-Aldama *et al.* conducted a study to compare the efficacy of BNT162b2 (Pfizer-BioNTech) vaccine in patients with cancer and the normal population. The results of their study revealed that the efficacy of one dose of the aforementioned vaccine was significantly lower in hematologic and solid organ cancer patients, as compared to the normal population.[98]

Consequently, it seems that we have to wait for more studies to know more about the efficacy, immunogenicity, and the best time of COVID-19 vaccination in patients with cancer who are under chemotherapy or radiotherapy. However, some guidelines have reported some instructions about vaccination in this group of patients and the time interval between vaccination and chemotherapy. These instructions are as follows:

1. It is recommended that the patients with cancer should be prioritized for the vaccination against COVID-19, and it is better to vaccinate them before the initiation of oncological therapy. It is better not to use live attenuated vaccines in immunocompromised patients. For now, no vaccine using this platform is available anywhere in the world.[99]
2. It is not routinely recommended that chemotherapy should be postponed or suspended.[100] The data regarding influenza vaccines and their booster shots have shown that the efficacy of the vaccine is not related to the time interval between vaccination and chemotherapy.
3. When B-cell-depleting agents such as anti-CD-20-antibodies (Rituximab) are being used, it is better to have a 6-month interval between consumption of these agents and COVID-19 vaccination to have the optimal response in the context of normal humoral immune system function.[101]

Conclusion

Pharmacotherapy should be done more carefully in the COVID-19 pandemic due to the lack of definitive treatment and many unanswered questions regarding multiple aspects of this mysterious virus. Some of the medications used in the urology field such as anti-androgens may protect the patients against the severe form of COVID-19. It seems that PDE inhibitors are beneficial as an adjuvant in controlling the respiratory symptoms of COVID-19. The level of immunosuppression and drug–drug interactions are of great importance among solid organ transplant recipients affected by SARS-CoV-2. It is suggested that ACEI medications should be continued in COVID-19 patients without any concern regarding their harmful effects.

Patients with urological cancers should receive the COVID-19 vaccine as soon as possible. In the case of solid urological cancer patients, evidence has shown the safety of COVID-19 vaccines; however, their efficacy might be lower than the normal population. Further research is needed to confirm such theories.

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