Prophylactic and early outpatient treatment of COVID-19 in patients with kidney disease: considerations from the Immunonephrology Working Group of the European Renal Association (ERA-IWG)

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SPECIAL REPORT

Prophylactic and early outpatient treatment of COVID-19 in patients with kidney disease: considerations from the Immunonephrology Working Group of the European Renal Association (ERA-IWG)

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic led to rapid vaccine development and large global vaccination schemes. However, patients with immune-mediated kidney disease, chronic kidney diseases and kidney transplant recipients show high non-response rates to vaccination despite more than three vaccinations and, consequently, reduced viral clearance capacity when infected while receiving certain immunosuppressants, carrying an elevated risk for coronavirus disease 2019 (COVID-19)-related morbidity and mortality. SARS-CoV-2 evolution has been characterized by the emergence of novel variants and spike mutations contributing to waning efficacy of neutralizing antibodies. To this end, the therapeutic field expands from vaccination towards a combined approach of immunization, pre-exposure prophylaxis and early post-exposure treatment using direct-acting antivirals and neutralizing monoclonal antibodies to treat early in the disease course and avoid hospitalization. This expert opinion paper from the Immunonephrology Working Group of the European Renal Association (ERA-IWG) summarizes available prophylactic and/or early treatment options (i.e. neutralizing monoclonal antibodies and direct-acting antivirals) of SARS-CoV-2-infected patients with immune-mediated kidney disease, chronic kidney disease and kidney transplant recipients.

Keywords: antiviral therapy, COVID-19, kidney, prophylaxis, transplantation

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has led to the rapid rollout of large

coronavirus disease 2019 (COVID-19) vaccination programs around the globe. Waning vaccine responses necessitate repeat vaccine doses but a subset of patients show lower levels of anti-S1 immunoglobulin G (IgG) levels as compared with controls, despite more than three vaccinations [1–4] and consequently, carry an elevated risk for COVID-19-related morbidity and mortality. This subset of patients includes, but is not limited to, patients with chronic kidney disease (CKD) [5–7], immunocompromised patients with immune-mediated kidney or rheumatic diseases [8, 9], or patients after solid organ transplantation (SOT) [10–16]. In immunocompromised patients, 28-day mortality due to COVID-19 remains higher than that of immunocompetent subjects [17]. In patients with ANCA-associated vasculitis, risk factors for severe COVID-19 were not only intense immunosuppressive therapy but also impaired kidney function, highlighting that a combination of risks adds to morbidity and mortality [18]. Mortality due to COVID-19 among kidney transplant recipients (KTR) remained high during the second half of 2020 when compared with non-transplanted patients [19]. Repeated vaccinations offer protection for severe COVID-19 [20] but some patients lack an adequate response. The most important risk factors for low vaccine response are older age (older than 65 years), immunosuppressive treatment, particularly with B-cell depleting agents and/or mycophenolate mofetil blunting SARS-CoV-2 vaccination-induced humoral response, whereas a strong vaccine response is seen in immunocompromised patients who were previously infected [21].

Neutralizing antibodies wane after vaccination in both immunocompetent and immunocompromised patients [22–24]. Also, in immunocompromised patients with a low response to vaccination, breakthrough infections occur [1, 25–28]. Despite effective vaccination in immunocompromised patients or KTR, reinfections often occur [29].

With societies globally opening again, the quality of life among many of these patients remains significantly impacted due to fears of contracting COVID-19 [30]. Importantly, the SARS-CoV-2 virus continues to mutate [31]. In most regions in the world, the Omicron variant is now dominant, especially the BA.4, BA.5 and BQ.1 subvariants with modified spike proteins [32] which are less well controlled by immune responses induced by the available Alpha-variant vaccines or previous COVID-19 episodes. Several studies have demonstrated the evolution of Omicron variants under immune pressure (neutralizing antibodies), enabling immune evasion through mutations [33–36], and these newer variants are less susceptible to the early generation neutralizing antibodies. A recent study among immunocompromised patients infected with Omicron and treated with the neutralizing SARS-CoV-2 monoclonal antibody sotrovimab found rapid development of resistance-associated mutations in up to half of subjects, associated with a significant delay in viral clearance [37]. On the brighter side, the Omicron strain appears to be associated with better outcome than its predecessors [38, 39].

Based on the reduced immunogenicity of SARS-CoV-2 vaccines in immunosuppressed patients, the therapeutic field expands from immunization towards a combined approach of vaccination, pre-exposure prophylaxis and early post-exposure treatment using direct-acting antivirals and neutralizing monoclonal antibodies in an attempt to treat early in the disease course and avoid hospitalization [40]. This opinion paper from the Immunonephrology Working Group of the European Renal Association (ERA-IWG) provides advice on which patients are at highest risk for hospitalization and/or complications and which in- and outpatient treatments can be considered.

GENERAL CONSIDERATIONS

In immunocompromised patients who contracted SARS-CoV-2, the first consideration is whether they can be treated in an ambulant setting. Patients who cannot take care of themselves or are oxygen dependent need to be hospitalized. In KTR with high risk of complications from COVID-19, reducing or stopping immunosuppressants should be considered as described previously by the DESCARTES working group [41, 42]. Fortunately, in the current phase of the pandemic, most KTR suffer from mild COVID-19 and as a result reducing immunosuppressants is not necessary. A similar picture is seen in other immunocompromised patients. Importantly, the Omicron era is characterized by lower mortality but for immunocompromised patients still higher than the rest of the population. Most studies reported here were performed during the pre-Omicron era or in patients suffering from Omicron strains up to BA.2 and not later whereas, currently, BA.5 and its subvariants are the dominant strains in Europe and North America. As a result, earlier data cannot directly be extrapolated to the current situation.

MONOCLONAL ANTIBODIES AGAINST SARS-CoV-2

Several monoclonal antibodies targeting the Omicron spike protein have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for emergency use in COVID-19 (Table 1). Of importance, due to loss of effective neutralization of activity against novel SARS-CoV-2 variants, the emergency-use authorizations for some compounds have already been withdrawn by the FDA. For instance, a recent *in vitro* study showed strongly diminished neutralization activity of sotrovimab for Omicron BA.2, BA.4 and BA.5 when compared with BA.1 [43].

Pre-exposure prophylaxis using neutralizing antibodies

Currently, only tixagevimab/cilgavimab is registered by the FDA for pre-exposure prophylaxis in high-risk patients (Table 1). Due to Fc modifications, tixagevimab/cilgavimab has an extended half-life of approximately 90 days, with levels detectable in serum for 9 months [44]. Tixagevimab/cilgavimab was first tested for pre-exposure prophylaxis in adults (≥18 years of age) in the PROVENT (Phase III Double-blind, Placebo-controlled Study of AZD7442 for Pre-exposure Prophylaxis of COVID-19 in Adult) (Table 2) [44]. This trial took place before the Omicron era and included unvaccinated

Table 1: Currently available SARS-CoV-2 monoclonal antibodies and antivirals and their *in vitro* efficacy against Omicron subvariants.

Monoclonal antibodies	EMA approved	FDA approved	Indication	*In vitro* Omicron neutralizing activity[c]
Sotrovimab	Y	N[a]	EOT	N
Casirivimab/imdevimab	Y	N[a]	HP	N
Tixagevimab/cilgavimab	Y	Y	PrEP	Y[b] (for BA.2, BA.2.12.1, BA.2.75, BA.4/5)
Regdanvimab	Y	N	EOT	N (only for BA.2.75)
Bebtelovimab	N	N[a]	EOT	Y (only for XBB, BQ.1, CH1.1)
Bamlanivimab	N	N[a]	EOT	N
Bamlanivimab/etesevimab	N	N[a]	EOT	N
Antivirals	EMA approved	FDA approved		Omicron effective
Remdesivir (Veklury)	Y	Y	EOT	Y
Nirmatrelvir/ritonavir (Paxlovid)	Y	Y	EOT	Y
Molnupiravir (Lagevrio)	Application submitted	Y	EOT	Y

[a]Until further notice.
[b]For BA.5 a higher dose was necessary, see main text for details.
[c]For most up-to-date information, see https://covdb.stanford.edu/susceptibility-data/table-mab-susc/.
Y =yes; N = no; EOT = early outpatient treatment; PrEP = pre-exposure prophylaxis; HP = hospitalized patients.

Table 2: Efficacy and safety data in large studies not focusing on immunocompromised patients.

Drug	Outpatients	PrEP	All data	AE	Data on ICP
Neutralizing antibodies					
Tixagevimab/cilgavimab [44]	Y	Y	RRR 76.7%; ARR 0.8%	35.3% vs 34.2%	Y
Tixagevimab/cilgavimab [104]	Y	N	RRR 50.5%; ARR 4.5%	29% vs 36%	Y
Regdanvimab [58]	N	N	HR 0.57 for oxygen need	27% vs 30.9%	N
Casirivimab/imdevimab [59]	Y	N	RRR 81.4%; ARR 6.3%	20.2% vs 29%	Y
Sotrovimab [57]	Y	N	Hospitalization 1% vs 7%	17% vs 19%	Y
Bebtelovimab [55]	Y	N	Hospitalization 1.6% vs 1.6%[a]	8.8% vs 7.8%[a]	Y
Bamlanivimab [54]	Y	N	OR 0.43	20.1% vs 18.9%	L [105]
Bamlanivimab/etesevimab [56]	N	N	RRR 70%; ARR 4.84%	14.7% vs 12.6%	N
Antivirals					
Remdesivir [78]	Y	N	HR 0.13 (symptoms)	42.3% vs 46.3%	Y
Nirmatrelvir/ritonavir [83]	Y	N	RRR 88.9%; ARR 6.2%	22.6% vs 23.9%	Y
Molnupiravir [93]	Y	N	HR 0.69 (hospitalization or mortality)	30.4% vs 33%	L

[a]Bebtelovimab mono versus placebo groups ($n = 11/125$ vs $n = 10/128$ in the double-blinded, low risk groups).
RRR = relative risk reduction of symptomatic COVID-19; ARR = absolute risk reduction; OR = odds ratio of COVID-19 incidence; HR = hazard ratio; Y = yes; N = no; L = limited; ICP = immunocompromised patients; PrEP = pre-exposure prophylaxis; AE = adverse events.

subjects who had an increased risk of an inadequate response to COVID-19 vaccination, an increased risk of exposure to SARS-CoV-2 or both. Briefly, 3460 patients received tixagevimab/cilgavimab and 1737 patients received placebo: SARS-CoV-2 infection occurred in 0.2% and 1%, respectively, with a relative risk reduction of 76.7% for symptomatic illness in favor of patients who had received tixagevimab/cilgavimab. Following this study, tixagevimab/cilgavimab was shown to neutralize the Omicron variant BA.1 *in vitro* [45] but only when using 600 mg instead of the earlier used 300 mg [46]. Importantly, the neutralizing efficacy of tixagevimab/cilgavimab is dose dependent, especially and more effectively in the BA.2 and BA.5 strains, as opposed to the BA.1 strain. Despite increasing dosages, tixagevimab/cilgavimab did not neutralize BA.2 and BA.5 as effectively as the ancestral Delta and B.1 strains [46]. Those *in vitro* data do not reflect clinical efficacy. The increasing escape of BA.5 to the efficacy of neutralizing antibodies such as tixagevimab/cilgavimab, resulting in lower maximum neutralization *in vitro*, is of concern for the future efficacy as new virus mutations arise [47]. Importantly, most data on tixagevimab/cilgavimab were collected in the pre-Omicron era and with the current high vaccination rate in developed countries, the number needed to treat to obtain a protective effect is uncertain.

Although included in the initial trial of tixagevimab/cilgavimab, patients with chronic kidney disease and immunocompromised patients had no events, therefore no conclusions could be drawn on the efficacy in this specific patient population [44]. In a large observational study in 1112 immunocompromised patients, tixagevimab/cilgavimab was administered as pre-exposure prophylaxis and the incidence of COVID-19 in these patients was compared with the general French population. Of 49 immunocompromised patients who had received tixagevimab/cilgavimab and contracted COVID-19 (4.4% of the total group), 43/49 had mild disease and 6/49 moderate to severe disease (of whom 2 died) [48] (Supplementary data, Table S1). Numbers were too low to make definite conclusions on the pre-exposure use of tixagevimab/cilgavimab. A retrospective observational study investigated pre-exposure prophylaxis of tixagevimab/cilgavimab in Israel during the BA.1 pandemic and included unvaccinated as well as vaccinated immunocompromised patients [of whom 36% were SOT recepients (SOTR)] who were treated with 300 mg intramuscular tixagevimab/cilgavimab. In the group that received tixagevimab/cilgavimab, 29/825 (3.5%) became infected as compared with 308/4299 (7.2%; $P < .001$) of the comparators, and 0/825 patients died as compared to 40/4299

Box 1. ERA-IWG recommendations for the prophylactic and early outpatient treatment of COVID-19 in patients with immune-mediated kidney diseases, CKDs and KTR

General recommendations:

- COVID-19 vaccine is recommended for all patients with immune-mediated kidney diseases, CKDs and for KTR because of these patients' increased risk of severe illness due to COVID-19. A third primary dose of COVID-19 vaccine is recommended to address the risk of lowered response or non-response to the standard two-dose schedule. Booster doses are more important for KTR since repeated vaccination is currently the only means to maintain high antibody levels.
- Immunocompetent vaccinated patients with CKD G3–5 not on dialysis probably do not benefit from treatment with SARS-CoV-2 monoclonal neutralizing antibodies or antivirals.
- Immunocompetent vaccinated patients on peritoneal dialysis or hemodialysis probably do not benefit from treatment with neutralizing antibodies and only benefit from treatment with antivirals in case of severe COVID-19.
- Patients with kidney disease should be considered for early treatment in an increasing manner with the presence of one or more (traditional) risk factors for developing COVID-19 complications [age >65 years, immunocompromised, lymphocyte depleted, diabetes mellitus, obesity, cardiac/pulmonary disease, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2] [41, 102].

Pre-exposure prophylaxis:

- In unvaccinated patients or patients without a vaccine response (undetectable or low neutralizing antibodies) who are at high risk for developing complications from SARS-CoV-2 infection, i.e. kidney transplant recipients and patients treated with rituximab, mycophenolate mofetil and/or cyclophosphamide, either unvaccinated or without a vaccine response after three or more vaccinations, prophylactic administration of Omicron-neutralizing antibodies, such as tixagevimab/cilgavimab or bebtelovimab, can be considered [49, 103].
- There is currently no role for antivirals in pre-exposure prophylaxis.
- There is currently no role for convalescent plasma in pre-exposure prophylaxis.

Post-exposure early outpatient treatment:

- There is currently no role for convalescent plasma in early outpatient treatment of patients with kidney disease.
- Patients who received rituximab before being vaccinated and did not have a vaccination response despite three or more vaccinations should be considered for administration of tixagevimab/cilgavimab or bebtelovimab.
- Patients who received rituximab after being vaccinated and/or have SARS-CoV-2 antibodies after vaccination or infection should be considered for treatment <5 days of symptom onset with nirmatrelvir/ritonavir or remdesivir or molnupiravir.
- Kidney transplant recipients who are at high risk for complications, i.e. patients who are either unvaccinated or without a vaccine response after three or more vaccinations, should be considered to receive tixagevimab/cilgavimab or bebtelovimab <5 days of symptom onset.
- In kidney transplant recipients who take calcineurin inhibitors (CNI) or mTOR inhibitors, the use of ritonavir should be approached carefully: interaction may potentiate high levels of CNI/mTOR inhibitors. As a result, the CNI/mTOR inhibitor should be withheld during the treatment of ritonavir (5 days) [87]. During that time corticosteroids should be increased. Forty-eight hours after the last dose of ritonavir, the CNI/mTOR inhibitor can be resumed. If neutralizing antibodies are unavailable, remdesivir (which is given intravenously) or molnupiravir (in that order) may be preferred over ritonavir-boosted compounds. Importantly, nirmatrelvir/ritonavir is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2.

in the control group (0.9%; $P = .005$) [49] (Supplementary data, Table S1). Another small study suggested that immunocompromised patients who did not respond to vaccination and received pre-exposure tixagevimab/cilgavimab were less likely to contract COVID-19 as compared with patients who did not receive neutralizing antibodies [50]. In a study of 933 vaccinated KTR, 113 (12.1%) contracted Omicron with most patients infected with BA.1. Patients who received tixagevimab/cilgavimab had fewer symptomatic infections (5.3%), lower hospitalization rate (1.5%) and lower mortality (0%), whereas transplant patients who had only received casirivimab/sotrovimab were not protected (26.9% symptomatic infections, 9.4% hospitalization and 3.1% mortality, respectively) (Supplementary data, Table S1) [51]. In summary, the exact impact of prophylactically administering tixagevimab/cilgavimab on mortality remains uncertain [52, 53], and therefore its pre-exposure administration should only be considered in immunocompromised patients who are either unvaccinated or did not have a vaccine response and thus are at high risk for COVID-19 complications (Box 1). In addition, the susceptibility of the prevalent SARS-CoV-2 strains for tixagevimab/cilgavimab should be checked, e.g. on https://covdb.stanford.edu/.

Early treatment with neutralizing antibodies

Several monoclonal antibodies have been tested in the early treatment of mild-to-moderate COVID-19 and most were shown to reduce COVID-19-related morbidity effectively and safely, and/or mortality [54–59] (Table 2). In studies

in immunocompromised patients, sotrovimab was effective during the earlier Omicron variants (BA.1) but in this study no control group of patients who did not receive sotrovimab was included [60]. Importantly, effectiveness of sotrovimab *in vitro* was lost over time due to the development of resistance, especially in immunocompromised patients [61–64]. Nevertheless, a Spanish observational study among 82 KTR showed lower COVID-19-related mortality in patients who received sotrovimab within 5 days after symptom onset as compared with those treated later [65]. The use of bamlanivimab in a small cohort of immunocompromised patients during the Omicron era appeared to result in escape mutations [66]. The mentioned study was too small to make definite conclusions.

Twenty-five SOTR (76% vaccinated) infected with Omicron received bebtelovimab (60% KTR) at an average of 3 days after symptom onset. Within 30 days, two patients had been admitted, one for pulmonary embolism and one for obstructive uropathy without respiratory complaints. From this observational study, bebtelovimab appeared safe and effective in avoiding disease progression and/or hospitalization [67]. Of note, bebtelovimab has been reported to maintain its neutralizing activity against the Omicron strains, including BA.5, *in vitro* [43, 68, 69]. However, a retrospective cohort study in Israel among SOTR (including 42% KTR) showed no difference between hospitalization or mortality when comparing early treatment with bebtelovimab versus sotrovimab during a time when the BA.1 and BA.2 strains were dominant [70].

As a result of waning efficacy of early generation neutralizing antibodies [71, 105–109], the development of newer neutralizing and/or combination antibody therapies may be necessary.

In summary, the impact of neutralizing monoclonal antibodies in the early outpatient treatment of COVID-19 on hospitalization and/or mortality remains unclear, especially in the light of the currently dominant BA.5 strain and subvariants. If used, it should be reserved for patients at high risk of complications and preferably administered within 5 days of symptom onset.

CONVALESCENT PLASMA

The use of convalescent plasma obtained from subjects who have recovered from COVID-19 has been shown to be effective in unvaccinated outpatients when given within 9 days of symptoms, preventing hospitalization [72]. Overall, however, a recent meta-analysis showed convalescent plasma to be of no additive value to prevent hospitalizations and COVID-19 complications [73]. In high-risk patients, a retrospective study in Germany found no benefit from convalescent plasma, and included immunocompromised patients [74]. An observational single-arm study from Brazil analyzed the use of convalescent plasma in KTR of whom the majority was treated in an outpatient setting (98.3% in the group who received convalescent plasma and 92.2% in the matched control group). There were no differences between the two groups considering need for oxygen, need for mechanical ventilation and/or death [75]. As a result, there is currently very limited evidence to administer convalescent plasma in an outpatient setting (Box 1).

DIRECT-ACTING SMALL MOLECULE ANTIVIRALS

Another class of drugs limits viral replication directly and has also been shown to be the most effective when used immediately after the onset of symptoms. This class includes the nucleoside analogs remdesivir (Veklury®), molnupiravir (Lagevrio®) and the protease inhibitor nirmatrelvir which is given together with ritonavir, a substance that inhibits metabolic clearance of nirmatrelvir (Paxlovid®) (Table 1).

Remdesivir, molnupiravir and nirmatrelvir/ritonavir remain active against the SARS-CoV-2 Omicron variant of concern and its sublineages [43, 76]. In line with this, a recent study from Israel on the outcomes of patients with COVID-19 who used nirmatrelvir during the Omicron surge confirmed its effectiveness: among patients 65 years of age or older, the rates of hospitalization and death due to COVID-19 were significantly lower among those who received nirmatrelvir than among those who did not [77].

PRE-EXPOSURE TREATMENT

There is no actual indication for antivirals in the setting of pre-exposure prophylaxis.

EARLY TREATMENT WITH ANTIVIRALS

Remdesivir

Remdesivir was one of the first antivirals to be tested in COVID-19 [78]. In a trial including 562 patients at high risk for disease progression, remdesivir was shown to reduce hospitalization rate and/or mortality by 87% as compared with placebo (Table 2) [78]. In a Spanish study including 98 KTR of whom 57 received remdesivir and 41 did not, hospitalization rate was higher in the remdesivir group (73.7% vs 29.3%). Mortality was reported lower in patients receiving remdesivir but it is important to note that among the group of subjects who did not receive remdesivir, 11 (26.8%) declined hospitalization and 26 subjects (63.4%) were more than 10 days after symptom onset, making the comparison difficult [79] (Supplementary data, Table S1). One prospective observational study during the Omicron BA.2 era included 192 SOTR with 41.7% KTR who were treated with a 3-day course of remdesivir within 7 days of symptoms, and reported an adjusted hazard ratio of 0.12 with an adjusted number needed to treat to prevent one hospitalization of 15.2. Although 90% of patients were fully vaccinated, early treatment with remdesivir may prevent hospitalization, intensive care unit admission and/or death [80].

Importantly, dosage of remdesivir may need to be adjusted according to kidney function. A small study in hospitalized patients with COVID-19 treated with remdesivir compared 115 patients with mild kidney impairment and 20 with severe kidney impairment and found no significant differences in liver

function tests or serum creatinine elevations due to remdesivir [81]. This may indicate that using remdesivir in patients with severe kidney impairment is probably safe and weighs up to the consequences of COVID-19 [110]. Finally, remdesivir was found to prevent hospitalizations during the Omicron surge (December 2021) in a retrospective single-center study including 82 immunocompromised patients (73.3% of total number of patients analyzed), mainly SOTR (odds ratio 0.41 when compared with no treatment); this study was too small to assess mortality [82].

Nirmatrelvir/ritonavir

Nirmatrelvir co-packaged with ritonavir was approved by the FDA in December 2021 for the treatment of mild-to-moderate COVID-19. Nirmatrelvir inhibits cleavage of polyproteins 1a and 1ab of SARS-CoV-2 and ritonavir blocks the CYP3A4 pathway, achieving higher plasma concentrations of antiviral agents. Nirmatrelvir/ritonavir was effective to avoid hospitalization in a study before Omicron [83] but remained effective in two studies performed in the Omicron era [77, 84]. Importantly, although the product monograph of nirmatrelvir states it is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2, Hiremath *et al.* suggest it may safely be considered in those patients based on their findings of pharmacology and toxicity [85]. In a small study among maintenance dialysis patients, a modified dose was shown to be safe and well tolerated [86]. The use of nirmatrelvir/ritonavir in SOTR may (pre-emptively) avoid COVID-19 complications and early reports support its safety [87, 88]. The ritonavir component may cause harmful interactions with other medication given its inhibition of CYP3A enzymes. This is especially relevant in the case of CNI and mTOR inhibitors which are frequently used in transplant patients [89]. The interaction between protease inhibitors reducing CYP3A4 activity and calcineurin inhibitors is well known and results in increased/toxic CNI levels [90]. Hence, when using nirmatrelvir/ritonavir in kidney transplant patients, the dosage of CNI or mTOR inhibitors should be reduced or stopped for 5 days and monitored by measuring trough levels more frequently [85, 87, 91]. It is currently unknown whether antivirals should be administered longer than the advised 5 days since rebound infections as well as rebound symptoms have been reported, especially in BA.5 [92]. This is of particular relevance in immunocompromised patients or KTR as their viral clearance is delayed, resulting in protracted viral replication.

Molnupiravir

Molnupiravir was first shown to be effective in ambulant patients with COVID-19 in the pre-Omicron era [93]. Early use of molnupiravir confirmed its efficacy in patients with Omicron [94]. One observational study [95] described a favorable outcome in nine previously vaccinated non-hospitalized KTR patients given ambulatory treatment with molnupiravir within the first 5 days after infection. Mycophenolate mofetil was tapered or discontinued in all patients. One patient was admitted to a general ward and there were no adverse events reported with its use. There were no significant interactions with calcineurin inhibitors. In a randomized controlled trial in the UK from 2020 to 2022 in an ambulant setting, 90 patients received molnupiravir and 90 patients received placebo [96]. Time to negative PCR for SARS-CoV-2 was shorter in patients receiving molnupiravir (8 versus 11 days) but not significantly so. These studies may indicate that molnupiravir is safe and possibly effective but larger trials are needed.

IMMUNOMODULATORS

There is currently no place for the use of immune-modulating agents such as kinase inhibitors, anti-interleukin-6 and/or anti-interleukin-1 for COVID-19 in ambulant patients. These agents have not been tested in pre-exposure setting or early treatment of SARS-CoV-2 infection.

CONSIDERATIONS BY THE ERA-IWG

The ERA-IWG provides an advice considering the individual patient care with kidney disease rather than an advice on public health care. The mutations of SARS-CoV-2 that occur as a result of administering monoclonal antibodies during an active infection are problematic and may result in loss of efficacy. Especially in immunocompromised patients in whom viral clearance is slow, more mutations develop [97, 98]. These patients may form a reservoir for SARS-CoV-2 and it is therefore important to improve viral clearance in individual patients to improve the outcome of the entire community. Although the use of current treatments results in mutations of SARS-CoV-2, especially in immunocompromised patients, if the treatment contributes to faster viral clearance, this may protect the community from further spreading of SARS-CoV-2 and there is thus a net beneficial effect. Direct antivirals have been shown to enhance viral clearance and reduce complication rates and these compounds may remain equally effective on new viral strains. However, a lack of data on efficacy of early treatment of COVID-19 in immunocompromised subjects as well as appearing viral resistance in these patients highlights the need for more studies. It is clear, however, that patients at very high risk of developing severe COVID-19 may benefit from neutralizing antibodies and/or antivirals. Patients with chronic kidney disease and immunocompromised patients have a high risk of developing COVID-19-associated complications where traditional risk factors (age >65 years, diabetes mellitus, obesity, number of comorbidities) accumulate with additional specific risk factors (low vaccine response due to immunosuppression, treatment with B-cell depleting agents) but an exact risk stratification remains to be made.

Currently, the National Institutes of Health (NIH) advises to administer tixagevimab/cilgavimab as pre-exposure prophylaxis to immunocompromised patients who are either unvaccinated or who did not have a vaccination response, and who are at high risk for COVID-19 complications such as hospitalization and/or death. Adequate seroconversion after vaccination is usually defined as obtaining an S1-IgG

concentration >10 binding antibody units (BAU)/mL, and an adequate response as S1-IgG concentration of 300 BAU/mL or greater (Supplementary date, Box S1) [99–101]. Also, in case of scarcity of certain treatments, the NIH advises to prioritize the use of COVID-19-directed treatments to vulnerable groups, including immunocompromised patients. In line with this, the ERA-IWG advises to only treat ambulant patients who are at very high risk for complications of COVID-19 with increased mortality rates.

KNOWLEDGE GAPS AND FUTURE PERSPECTIVES

Although the management of the COVID-19 pandemic appears to be improving globally, many uncertainties remain for patients with immune-mediated kidney disease, CKDs and kidney transplant recipients. Mutations of SARS-CoV-2 may result in a new approach where the choice of administering neutralizing antibodies and/or treating with antivirals will be patient tailored. Consequently, there is a need for continuous genomic surveillance in immunocompromised patients to address the expanding antigenic diversity and subsequent emergence of resistance during COVID-19 treatment.

In addition, the optimal dosing and routes of administration in different stages of CKD remain to be determined. We will need to investigate individual cost–benefit assessments in CKD patients, based on individual risk profile for severe COVID-19. Finally, studies investigating combination therapy with neutralizing monoclonal antibodies and direct-acting antiviral compounds will need to be performed to protect CKD patients from complications of COVID-19.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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