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Opinion of the AVATHER group of 19 October 2023

Response to COVARS' request for a supplementary opinion on the various treatments for early-stage COVID-19

The latest recommendations issued in the spring of 2023 in France recommended first-line nirmatrelvir/ritonaviritonavir (Paxlovid®), second-line remdesivir (Veklury®) and third-line sotrovimab (Xevudy®) for early treatment of COVID-19. These recommendations were based on existing clinical data and in a context where the circulating sub-variants were essentially BA.4 and BA.5. Epidemiological developments since then, as well as new efficacy and safety data published in the meantime, justify updating these recommendations.

An update on the circulation of classified variants in France

The current circulation of SARS-CoV2 in France has been characterised by a steady increase in its detection in respiratory samples since July 2023. The rate of detection of SARS-CoV2 in hospitals participating in the RENAL network rose from 4.72% at the beginning of July 2023 to 17.24% at the beginning of September 2023 (CNR des Virus Respiratoires).

The study of circulating variants is based on weekly Flash Tests, the results of which are analysed jointly by Santé Publique France and the National Reference Centres for respiratory viruses.

For more than a year, global circulation of SARS-CoV2 has been dominated by the Omicron variant and its sublineages, which are highly transmissible, less severe in clinical expression (except in subjects identified as being at risk), and exhibit immune escape, enabling viral circulation to be maintained in the population. At present, recombinant XBB is the most widely detected virus worldwide, with genetic diversification continuing within the various sub-lineages. Three variants have been classified as VOI (variants to watch) by the WHO, with the following detection rates in France at the end of September 2023: 9% for variant XBB.1.5, 14% for variant XBB.1.16, and 42% for variant EG.5.

EG.5 is a sublineage of XBB.1.9 and has the F456L mutation in surface protein S. The first sequences of EG.5 deposited on GISAID date back to February 2023, and its detection has increased in several regions of the world (Asia / Europe / North America). At the end of September, it represented 38 % of the sequences deposited on GISAID worldwide.

Among the other sub-lineages of the Omicron variant that continue to circulate at low levels, several are classified as VUM (variants under evaluation), including the BA2.86 variant, which is the subject of particular surveillance due to its genetic profile. At the end of September 2023, this variant represented less than 1% of the sequences deposited on GISAID, with a sampling date between 26 August and 25 September 2023. Most of these sequences come from the United Kingdom (N=52), Denmark (N=27), the United States (N=20), South Africa (N=18) and Sweden (N=18). This variant is thought to have emerged in June 2023, with a low-noise global spread, as shown by the numerous reports of detection of BA2.86 in wastewater in many countries (UK Health Security Agency, 2023). This variant therefore circulates within a mixture of antigenically distinct variants, with apparently higher immune escape capacities. It is therefore plausible that this variant will become dominant, although it is not really possible to predict this at present.

The BA2.86 variant carries 33 mutations in the S protein, including 14 in the RBD (*Receptor Binding Domain*) compared with its most plausible ancestor BA.2. An unusual number of mutations have also been identified in the N-terminal part of the S protein. These numerous mutations could correspond to an "evolutionary leap" generating a major wave of SARS-CoV2 contamination *via* increased transmissibility, increased replicative capacity and escape from existing therapies.

Review of the severity of COVID-19 in the current epidemiological context

On the basis of an analysis carried out in early 2023, it was observed that, depending on the location, vaccination coverage rates, healthcare resources and criteria used, the "gross" severity observed in the Omicron era was 2 to 10 times lower overall than in the Delta era (without adjusting for the degree of protection of the population, which has increased over time) (AvATher opinion, January 2023).

New studies have corroborated this observation. A recent meta-analysis of 33 studies including 6,037,144 patients treated with COVID-19 during the Delta and Omicron periods concludes that infection with Omicron is associated with a reduced risk of hospitalisation (OR = 2.95; 2.35-3.60), admission to intensive care (3.64; 2.63-5.04) or death (OR = 2.97; 2.17-4.08). It should be noted that the death rate in the Omicron era was 0.46% in the general population, and 7.10% in hospitalised patients (Hu et al. 2023).

A recent German study also shows that the risk of in-hospital mortality remains higher with Omicron than with influenza (OR = 1.56, IC95% 1.32-1.84) (Dickow et al. 2023).

Reassessment of groups at risk and at very high risk of severe COVID-19

The definition of groups particularly at risk of an unfavourable outcome was established on the basis of the first studies, in the first wave in particular.

The reassessment of the severity observed during the Omicron era at the beginning of 2023 in the various published studies led to the conclusion that, although the overall severity of COVID-19 was significantly less than during the first waves (see above), the risk factors for severity remained the same (AvATher opinion January 2023).

With regard to age, the vast majority of studies showed the benefit of early treatment (most often nirmatrelvir/ritonaviritonavir) in people aged over 65, and even more so in patients aged 80 and over (excess risk of severe forms 8.12 [7.89-8.35] (Aggarwal et al. 2023) and mortality of 5.453 [4.966-5.989] (Colnago et al. 2022) in patients aged > 80). All but one (Wong et al. 2022) demonstrated this benefit, including in fully vaccinated people over 65. Furthermore, in the study that included the largest number of patients (Shah et al. 2022), this benefit in people over 65 was only significant in those with at least one associated comorbidity. In people under 65, the results of the studies were divergent. When a significant benefit was observed, it was less than in the older population and concerned only those under 65 with at least one comorbidity (Shah et al. 2022). The results of a US study published since then (Aggarwal et al. 2023) also support a benefit of early treatment in the under-65s (adjusted OR for hospitalisation = 0.53, CI95% 0.34-0.80), with an overall risk that falls from 1.0% without treatment to 0.7% with).

As for the other risk factors considered individually, the observational studies published recently do not allow us to reassess their 'weight' and refine the definition of groups at risk or at very high risk of severe forms of COVID-19 in the era of new sub-variants.

However, population-based analyses such as an English study published in 2023 involving more than 1,200,000 people (Hippisley-Cox et al. 2023) make it possible to refine the assessment of the risk of hospitalisation or death linked to COVID. As a result of the reduction in the severity of COVID-19 observed with the new variants in a largely vaccinated and/or immunised population, the number of subjects to be treated to avoid an event increases. Taking as a basis of reasoning a reduction in the risk of hospitalisation or death from 1.5% without therapeutic intervention to 1% after therapeutic intervention (estimate based on the efficacy observed with current options), around 200 people would need to be treated to avoid hospitalisation. This estimate tallies with those in the Omicron literature (Wee et al. 2023; Weiss 2023). The number of people who would need to be treated to avoid hospitalisation or death during the Omicron period is probably lower for the population most at risk. In the case of immunocompromised individuals, it has very recently been estimated at between 16 (Kaboré et al. 2023) and 42 (Wee et al. 2023).

This means that treatment efforts should be particularly focused on **patients at very high risk**, who are still the most vulnerable:

- solid organ transplants,
- treated by allogeneic haematopoietic stem cell transplantation,
- with cancer and haematological malignancies undergoing chemotherapy within the last 12 months,
- treated with immunosuppressants (including corticoids and anti-CD20)
- with severe chronic kidney disease (GFR < 30mL/min), including dialysis patients,
- with chronic poly-pathologies and at least two organ failures,
- living with HIV with a CD4 count < 200/mm^3 ,
- suffering from certain rare diseases and at particular risk of infection (Filières de Santé Maladies Rares 2020)
- with trisomy 21
- with primary immune deficiency
- aged > 80 and booster vaccination more than 6 months old

People considered to be at **high risk** should also be able to benefit from these measures. These people meet at least 2 of the following conditions:

- COVID vaccination: none or booster more than 6 months old
- age > 65
- treated type 1 or 2 diabetes
- obesity (BMI > 30 kg/m)^2
- respiratory insufficiency from any cause, severe COPD, pulmonary fibrosis
- chronic renal failure
- ischaemic heart disease, hypertension and/or heart failure
- chronic liver disease or cirrhosis
- history of stroke, dementia, psychiatric disorder
- severe haemoglobinopathy

Preclinical data on the activity of antivirals on new circulating variants

Direct antivirals

Since the EG.5 sub-variants and the BA.2.86 VUM have not acquired key mutations in either NSP5 or NSP12 (Kaku et al. 2023; Uriu et al. 2023), the antiviral activity of nirmatrelvir and remdesivir should be preserved, as it was for XBB.1.5 (Uraki et al. 2023) and BA.2 (Takashita et al. 2022).

Sotrovimab

For the record, sotrovimab exerts its antiviral action by 2 mechanisms: viral neutralisation and antibody-dependent cytotoxicity against targets expressing SARS-CoV2. This has been demonstrated in particular against BQ.1.1 and XBB.1.5 variants (Addetia et al. 2023; Bruel et al. 2023).

Data available in preprint suggest that sotrovimab retains activity at least equivalent to previous XBB variants against EG.5 sub-variants (XBB.1.9.2 + S:F456L), which are currently in the majority in France (Uriu et al. 2023; Q. Wang et al. 2023). Animal models (hamster and macaque) have also shown that sotrovimab retains activity against BQ.1.1 (Driouich et al. 2023; Hérate et al. 2023).

Concerning the variant under surveillance (VUM) BA.2.86, the available data, obtained with pseudo-typed viruses, suggest a new loss of sotrovimab activity (Uriu et al. 2023; Yang et al. 2023). The BA.2.86 variant in fact has the K356T mutation in the S protein, which drastically reduces the binding and neutralising activity of sotrovimab (Addetia et al. 2023).

Reassessment of the efficacy and clinical safety of nirmatrelvir/ritonavir (Paxlovid®) in 2023

Real-life efficacy data

Several studies had confirmed the efficacy of nirmatrelvir/ritonaviritonavir in the Omicron period with BA.1 and BA.2 sub-variants, with a reduced relative risk of hospitalisation and/or death (from 0.21 to 0.56), in a predominantly vaccinated population. The observed rates of hospitalisation or death ranged from 0.56 to 2.7% with nirmatrelvir/ritonavir versus 0.96 to 4.1% without treatment (or 0.015-0.016 versus 0.029-0.059/100 person-days) (Arbel et al. 2022; Bajema et al. 2023; Dryden-Peterson et al. 2023; Najjar-Debbiny et al. 2023; Schwartz et al. 2023; Shah et al. 2022). The results of these studies supported the recommendation to use nirmatrelvir/ritonaviritonavir as first-line treatment for early outpatient treatment of COVID-19 in people at risk.

Other studies on the Omicron BA.1 or BA.2 period have since been published in the same vein:

- An Italian national study (Torti et al. 2023) evaluated 11576 patients treated with nirmatrelvir/ritonavir compared with 17977 patients treated with molnupiravir between February and April 2022. Most patients (86.7%) were fully vaccinated. The adjusted incidence rate of mortality observed was 0.78% (0.58%-0.98%) in the nirmatrelvir/ritonavir group versus 1.23% (1.07%- 1.38%) in the molnupiravir group (adjusted log rank p = 0.0002).
- A retrospective Welsh study (Evans et al. 2023) comparing nirmatrelvir/ritonavir, molnupiravir and sotrovimab with no treatment in 7013 very high-risk patients, found that

showed an overall reduction (35%, 95% CI 18-49%) in the risk of hospitalisation or death in treated patients compared with untreated patients, with no difference observed between the 3 types of treatment.

New studies in the Omicron sub-variants BA.4 and BA.5 period confirm the effectiveness observed in real life:

- A US observational study (Lewnard et al. 2023) in the Omicron period (BA.2, BA.4 and BA.5) compared 7274 patients treated with nirmatrelvir/ritonavir (5472 of whom were tested within the first 5 days of symptoms) with 126152 untreated patients (84657 of whom were tested within the first 5 days), the vast majority of whom had been vaccinated (94.6 and 86.7% with at least one dose, and 80.6 and 60.1% with at least 3 doses, respectively). It reported an efficacy rate of 53.6% (IC95%: 6.6-77%) in preventing hospitalisation or death within 30 days, irrespective of the delay in initiating treatment in relation to the onset of symptoms, of 79.6% (IC95%: 33.9-93.8%) for those treated within the first 5 days, and of 66.5% (IC95%: 24-85.3%) for those who received at least 3 doses of vaccine. This study confirms the efficacy in high-risk patients (51.6 % or 81.2% if administered within 5 days), but without being able to detail the impact according to the type of underlying comorbidity.
- Another study conducted in Colorado (USA) during the Omicron period (including waves BA.4 and BA.5) compared 9881 patients treated with nirmatrelvir/ritonavir with 11612 untreated patients, with propensity score analysis (Aggarwal et al. 2023). Nearly 80% of patients had received at least one dose of vaccine, and nearly 60% at least 3 doses. The risk of hospitalisation or death at D28 was significantly reduced in the nirmatrelvir/ritonavir group (OR = 0.45; 95% CI 0.33-0.62 and OR = 0.15; 95% CI 0.03-0.50, respectively). In an adjusted sub-group analysis, the benefit remained significant, particularly in people aged under or over 65, vaccinated or not, and suffering from at least one comorbidity. However, the difference was no longer significant in people with no co-morbidity (obesity, cardiovascular disease, diabetes, lung disease or liver disease, i.e. 38.9% of people treated). No differences in efficacy were observed according to the period of predominance of BA.1/BA.2 or BA.4/BA.5.
- A Hong Kong study during the Omicron period (Lui et al. 2023) focused on 793 people with type 2 diabetes treated early with nirmatrelvir/ritonavir, nearly 58% of whom had received at least 3 doses of vaccine, and matched them with 793 untreated diabetics. The risk of hospitalisation and/or all-cause mortality was reduced in the nirmatrelvir/ritonavir group (OR = 0.71; IC95%: 0.63-0.80).
- A retrospective Quebec study assessed the impact of nirmatrelvir/ritonavir in 8402 patients matched to 8402 controls on propensity score, in periods BA.2, and BA.4/5 (Kaboré et al. 2023). Irrespective of vaccination status, the risk of hospitalisation was significantly reduced (RR = 0.31; 0.28-0.36). The benefit observed was greater in patients whose primary vaccination was incomplete, but was no longer significant in those who were fully vaccinated, unless they were severely immunocompromised.
- A recent cohort study (including XBB and BQ.1) evaluated the efficacy of nirmatrelvir/ritonavir in 22,594 patients, with a reduction in the risk of hospitalisation or death (adjusted HR 0.63, IC95% 0.59-0.68) compared with no treatment, regardless of age, sub-variant, vaccination status or co-morbidities (Lin et al. 2023).
- A recent Singaporean study including 3959 patients treated with nirmatrelvir/ritonavir and 139379 controls during the different Omicron waves, including XBB, most of whom (95%) were well vaccinated, also showed a reduction in the risk of hospitalisation (ORaj = 0.65; 0.5-0.85) (Wee et al. 2023). However, there was no significant reduction in the already very low risk of severe disease (0.3%).

These studies, even though clinical efficacy data are limited with the latest Omicron sub-variants (in particular BA.4, BA.5, XBB, BQ.1, EG5, etc., see above), confirm the clinical efficacy of Omicron.

nirmatrelvir/ritonavir up to BA.4 and BA.5, with a reduction in the risk of hospitalisation that appears to be close to 50%, and probably more in the risk of death.

Tolerability data in cases of renal impairment

Several studies have evaluated the pharmacokinetics and safety of nirmatrelvir/ritonavir in patients with severe chronic kidney disease (GFR < 30ml/min) and/or haemodialysis (Chun et al. 2023; Hiremath et al. 2023; Lingscheid et al. 2022; Lu et al. 2023). By reducing the dose of nirmatrelvir/ritonavir (with different therapeutic regimens depending on the study or the patient (300/100 mg D1 then 150/100 D2-J5, or (150 or 300)/100x2 D1 then 150/100x2, or 150/100 D1-J5, or 150/100 D1 D3 D5), these studies conclude that there is an increase in plasma concentrations, which may remain within the limits observed in normorenal patients, and without accumulation or significant safety signals after 5 days' treatment. Virological efficacy appears to be preserved in most studies, except in one, despite high plasma concentrations (Lu et al. 2023). The two largest studies in terms of numbers, including 134 Canadian patients (Hiremath et al. 2023) and 59 Hong Kong dialysis patients (Chun et al. 2023) observed that 96% and 94.1% of patients completed the 5-day treatment period, respectively.

Overall, with the treatment regimen most frequently evaluated, i.e. 300/100 mg once daily on D1 followed by 150/100 mg once daily on D2-J5, nirmatrelvir/ritonavir appears to be a feasible therapeutic option for patients with severe chronic renal failure and/or haemodialysis. Given the heterogeneity of the studies, this off-label option should only be considered after an individual assessment of the benefit/risk ratio, in the absence of a satisfactory and/or available alternative. Furthermore, as pharmacological data is scarce, it is recommended that assays be performed whenever possible.

Safety data in pregnant women

The limited clinical data available on the use of nirmatrelvir/ritonavir in pregnant women is reassuring (Chourasia et al. 2023; Siberry et al. 2022). However, the number of patients is limited, making it impossible to formulate a recommendation for this population at the present time.

Reassessment of the clinical efficacy and safety of remdesivir (Veklury®) in 2023

Real-life efficacy data

The randomised controlled double-blind PINETREE trial prior to the Omicron period demonstrated the efficacy of early remdesivir use in at-risk individuals in preventing hospitalisations and deaths (OR = 0.134; 95% CI 0.031- 0.586) (Gottlieb et al. 2022).

An initial retrospective study in the United States, conducted in part during the Omicron BA.1 period and including 260 high-risk patients treated early, showed a reduction in the risk of emergency room visits or hospitalisation (OR = 0.41, 95% CI 0.17-0.95) in those treated early with remdesivir (Piccicacco et al 2022).

A new Italian observational study assessed the efficacy and safety of remdesivir used early in COVID-19 (Mazzitelli et al. 2023). It included 316 patients treated early with remdesivir (79.1% vaccinated) who were compared with 365 patients who refused early treatment (52.9% vaccinated). The early use of remdésivir according to the 200 mg D1

then 100 mg on D2 and D3 reduced the risk of hospitalisation (adjusted OR = 0.049; IC95% 0.012-0.16). Among treated patients, 1.6% experienced adverse events attributed to remdesivir (all digestive and grade 1).

Another prospective Spanish study (Aiello et al. 2023) including 60 patients with haematological malignancies between December 2021 and March 2022, treated early with remdesivir alone or in combination (53%) for 5 to 10 days (median 9 days), showed a mortality attributable to COVID-19 of 0% (5% all-cause mortality), with good safety. There was no comparator group.

Other recently published studies, while not giving negative signals in terms of safety, do not provide fully usable information on the clinical efficacy of remdesivir in the early phase. In the international retrospective study including 3010 patients aged over 65 (Margalit et al. 2023), with an inclusion period running from January 2020 to May 2021, no sub-analysis was presented for the Omicron period, as most patients also required oxygen therapy. Another multicentre US study compared 19184 patients treated with remdesivir with 11213 not treated, but in hospitalised patients. A reduction in mortality was observed at 14 days (OR = 0.70; IC95% 0.62-0.78) and 28 days (OR = 0.75, IC95% 0.68-0.83). This benefit was also observed during the Omicron period (OR = 0.75; 0.63-0.90 and OR = 0.84; 0.72-0.97, respectively) (Mozaffari et al. 2023).

A few cohort studies reporting an indirect comparison between remdesivir and nirmatrelvir/ritonavir in the Omicron period suggest greater efficacy of the latter. An Italian prospective study included 562 at-risk patients, 252 of whom were treated with nirmatrelvir/ritonavir and 196 with remdesivir (Tiseo et al. 2023). The rates of hospitalisation or death were 0.8% and 5.1
%, respectively, suggesting greater efficacy with nirmatrelvir/ritonavir. A Greek study (Basoulis et al. 2023) compared a prospective cohort of 356 remdesivir-treated patients with 165 nirmatrelvir/ritonavir-treated patients, weighted by inverse probability (IPTW). While being vaccinated was associated with a reduced risk of hospitalisation within 30 days, no difference was observed this time between remdésivir and nirmatrelvir/ritonavir (30-day hospitalisation rates of 2.8% and 3.0%, respectively).

Tolerability data in cases of renal impairment

The randomised, double-blind, placebo-controlled phase 3 REDPINE trial included 263 people with COVID-19 and a glomerular filtration rate of less than 30 ml/min/1.73m², with a $_{Sa02}$ of less than 94% (Santos J.R. et al, 2023). Of these, 37% were on dialysis. Participants were randomised 2:1 to receive remdesivir (200 mg D1 then 100 mg D2-D5) or placebo. Although plasma levels of the main metabolite (GS-441524) or the excipient (SBECD) were increased in the remdesivir-treated group, the rate of adverse events did not differ between the groups, including serious adverse events.

A sub-study of the CATCO trial (Cheng et al. 2022) assessed the safety of early remdesivir in 34 people with creatinine clearance of less than 30 ml/min. The change in glomerular filtration rate in this study did not differ significantly from that observed in the 25 people with a baseline clearance of less than 30 but not treated with remdesivir.

In another retrospective single-centre US study involving 31 people with a baseline clearance of less than 30 treated with remdesivir, glomerular filtration rates measured at the end of remdesivir treatment tended to be higher than before (18 vs 15, p<0.001) (Stancampiano et al. 2022). In addition, there was no significant movement in bilirubin.

These factors have led the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) to issue a favourable opinion on extending the use of remdesivir to

COVID-19 in stage 4-5 CKD patients with or without dialysis, an opinion endorsed by the EMA on 26 June 2023. This extension was also validated by the FDA on 14 July 2023.

Safety data in pregnant women

Clinical data are limited, but to date have not demonstrated any toxicity in pregnant women. This limited data does not allow a recommendation to be made for this population at present.

Reassessment of the clinical efficacy of sotrovimab (Xevudy®) in 2023

Few real-life data are available on the efficacy of sotrovimab; the available data concern variants up to BA.5 but not beyond. These observational data (with their limitations) suggest that sotrovimab is effective in reducing the risk of severe forms.

An Italian retrospective study conducted between 1/1/22 and 31/12/2022 analysed 341 patients who had received sotrovimab compared with 348 untreated patients (De Vito et al. 2023). These 2 groups differed in age (slightly younger in the sotrovimab group, 71 vs. 75 years) and in the proportion of immunosuppressed patients and organ transplant recipients (respectively 33% and 7% in the sotrovimab group vs. 11% and 1.7% in the untreated group). In multivariate analysis, the risk of oxygen use and the risk of death were increased by age (OR = 1.23, CI95% 1.04-1.45; OR = 1.36, CI95% 1.09-1.69, respectively) and decreased by sotrovimab treatment (OR = 0.05, CI95% 0.02-0.11; OR = 0.16, CI95% 0.06-0.42 respectively). The risk of mortality was also reduced by vaccination (OR = 0.37, CI9% 0.20-0.68).

Data from the English cohort in the Opensafely platform were collected from February to October 2022, i.e. over a period of circulation of the omicron BA.2 to BA.5 sub-variants. A total of 7863 eligible patients were analysed: 4836 on nirmatrelvir/ritonavir and 2847 on sotrovimab. Propensity score analysis showed a similar risk of progression or death in these 2 treatment groups. At D28, 52 (0.68%) COVID-19-related hospitalisations/deaths were observed: 33 (0.68%) in the nirmatrelvir/ritonavir arm and 19 (0.67%) in the sotrovimab arm. Very few COVID-related deaths were observed: 8 in the nirmatrelvir/ritonavir arm and ≤5 in the sotrovimab arm (Zheng et al. 2023).

In the retrospective US study, partly in the Omicron BA.1 period and including 260 high-risk patients treated early, both remdesivir (OR = 0.41; 95% CI 0.17-0.95) and sotrovimab (OR = 0.28; 95% CI 0.11-0.71) reduced the risk of emergency room visits or hospitalisation, and the sotrovimab group (Piccicacco et al. 2022).

However, there is a risk of the emergence of sotrovimab-resistant variants in immunocompromised patients (transplant patients or haemophiliac patients), 27.8% of whom (12/43) have prolonged excretion of SARS-CoV2. Mutations emerged in 32.6% of patients treated as monotherapy with sotrovimab, reducing sensitivity to sotrovimab in a neutralisation test using pseudoviruses (Gliga et al. 2023).

Other treatment options

a) Other options of potential and available interest

- **Plasma from convalescents**

Although several studies have evaluated the potential benefit of Covid convalescent plasma (CCP) in patients with prolonged viral excretion and/or severe forms of the disease, there is little recent data from the Omicron period on this therapeutic option for the early treatment of minimal or moderate forms of COVID-19. A Cochrane "meta-analysis" of 2 therapeutic trials in patients with minimal forms did not show any benefit in terms of clinical course, risk of hospitalisation or death (Iannizzi et al. 2023).
Regardless of these results or lack of evidence, the use of these PCCs raises issues of quality (the need for high titres of neutralising antibodies against circulating sub-variants), availability and/or logistics in order to use them rapidly. Further studies are therefore needed to establish their potential value.

- **Therapeutic combinations**

Combination therapies have been relatively little evaluated in the early treatment of COVID-19. A few preliminary retrospective studies suggest a possible benefit from a combination of remdesivir and monoclonal antibodies (Hirai et al. 2023), remdesivir and convalescent plasma (Magyari et al. 2022), or remdesivir and paxlovid (Blennow et al. 2023). The methodological limitations and the variability in the antiviral activity of monoclonal antibodies or convalescent plasma depending on the variants involved mean that it is not possible to draw conclusions and recommendations for management. A therapeutic trial evaluated the benefit of a combination of remdesivir and interferon beta-1b vs remdesivir alone, for 5 days, in 212 patients with a median age of 65 and comorbidities in 75% of them (Tam et al. 2023). It should be noted that these patients were all hospitalised, even though almost 90% had a Sa02 ≥ 94% and a median time to onset of symptoms of 2.5 days. Although a virological and clinical benefit (time to return to a NEWS2 score of 0) was observed in the dual therapy group, no deaths were observed in either group.
A randomised controlled trial is currently underway (OPTICOV - ANRS-MIE / Geneva University Hospitals) to assess whether antiviral therapy combining two direct antivirals (nirmatrelvir/ritonavir + remdesivir) and/or an increase in the duration of nirmatrelvir/ritonavir from 5 to 10 days improves antiviral efficacy at D10.

b) Treatments of potential interest that are not available

- **Molnupiravir (Lagevrio®)**

The results of studies on the real-life efficacy of molnupiravir are heterogeneous, particularly in the Omicron period. Some studies (notably in Hong Kong) showed a benefit with a reduction in the risk of hospitalisation or death, in some cases close to that observed with nirmatrelvir/ritonavir (Cowman et al. 2023; Evans et al. 2023; Lin et al. 2023; Lui et al. 2023; Wan et al. 2023), while others reported lower clinical efficacy than nirmatrelvir/ritonavir (Gentile et al. 2022; Torti et al. 2023), and some showed no significant effect (Bajema et al. 2023; Flisiak et al. 2022; Wong et al. 2022), including the UK platform trial PANORAMIC (Butler et al. 2023).

A recent meta-analysis including 14 trials with 34570 patients (Sun et al. 2023) concluded that there was a significant reduction in the risk of hospitalisation (RR = 0.63; 0.47-0.85) or mechanical ventilation (RR = 0.37; 0.19-0.72), but not in the risk of mortality (RR = 0.40; 0.10-1.53).
In virological terms, the randomised phase 2 PLATCOV trial (Schilling et al. 2023) showed that viral clearance was less rapid with molnupiravir than with nirmatrelvir/ritonavir, with a higher mutation rate in the event of viral persistence (not observed with nirmatrelvir/ritonavir). Another recent study reports the possibility of selection of mutated viruses in patients treated without viral eradication, possibly leading to greater persistence due to easier escape from the immune response (Sanderson et al. 2023). This could explain why, in the PANORAMIC trial, the SARS-Cov2 viral load was lower on molnupiravir at D5, but higher at D14. The impact on the transmissibility of these mutated viruses also remains to be established.

The application for authorisation of molnupiravir (Lagevrio®) at European level was withdrawn on 21 June 2023, following an assessment of the dossier and a recommendation by the European Medicines Agency (EMA) to refuse authorisation, due to the impossibility of concluding that there was a reduction in the risk of hospitalisation or death in adult patients at risk of severe forms of the disease.

This treatment is therefore not available in France.

- **Ensitrelvir**

Ensitrelvir is an inhibitor of the 3C like protease of SARS-CoV2, with pharmacokinetic characteristics that mean it does not need to be combined with a "booster". However, it is a potent inhibitor of CYP3A (Shimizu et al. 2023), and significant interactions are therefore possible with molecules that are substrates, inhibitors or inducers of CYP3A. Furthermore, *in vitro* and *in vivo* studies suggest that certain mutations confer resistance to ensitrelvir. Their current prevalence appears to be low, but it is important to monitor their occurrence (Ip et al. 2023; Kiso et al. 2023).

Its efficacy was evaluated in a phase 2b/3 trial, with 1:1:1 randomisation (ensitrelvir 125 mg, ensitrelvir 250 mg: placebo), once a day for 5 days in 341 people with mild to moderate forms of COVID-19) (Mukae et al. 2023). The study was conducted during the Omicron BA.1 period. The vast majority of participants were aged between 18 and 65, 85% had received at least one dose of vaccine, and 31% were hospitalised at the time of inclusion. While a virological benefit was observed with ensitrelvir, no clinical benefit was observed in terms of the "global" evolution of symptoms. These data provide no information on the efficacy of ensitrelvir in elderly or at-risk patients. A phase 3 trial is currently being conducted in this population (SCORPIO-HR trial).

- RAY1216

RAY1216 is also an inhibitor of the 3C like protease of SARS-CoV2. A phase 2 trial was conducted in China at the peak of the Omicron pandemic in China, including patients who had been infected with COVID-19 for 5 days or less (Wang et al. 2023). Half of the participants (n=30) were randomised 2:1 to receive RAY1216 or placebo, while the other half were randomised 2:1 to receive ritonavir boosted RAY1216 or placebo. The 2 placebo groups were pooled for analysis. Viral clearance was observed to be more rapid in patients treated with RAY1216 (boosted or not), with a gain of just over 4 days. No significant clinical impact was observed in patients who were predominantly young and vaccinated. A phase 3 trial is currently underway in China.

- VV116

VV116 is an oral derivative of remdesivir. Its efficacy was evaluated in a randomised phase 3 trial compared with unblinded nirmatrelvir/ritonavir (Cao et al. 2023). A total of 367 patients on VV116 were evaluated and compared with 374 on nirmatrelvir/ritonavir (24% unvaccinated). It was concluded that VV116 was virologically and clinically non-inferior to nirmatrelvir/ritonavir, although the clinical criterion used, speed of symptom resolution, remains fairly subjective and the lack of blinding to the treatment received is a major limitation. Further studies are therefore needed before this potential therapeutic option can be considered.

- **Interferon lambda**

Between June 2021 and February 2022, the TOGETHER platform trial evaluated the benefit of subcutaneous interferon lambda 180 ug in 933 people with mild to moderate COVID, compared with 1018 treated with placebo (oral or injectable) (Reis et al. 2023). The trial was conducted almost exclusively in Brazil, most of the participants had received at least one dose of vaccine, and 40% were infected with an Omicron variant (BA.1). However, the SARS-CoV2 seropositivity rate was higher in the interferon group than in the placebo group (87% vs. 70%). The study concluded that there was a reduced risk (OR = 0.49; CI95% 0.30- 0.76) of reaching the composite endpoint, which was either hospitalisation or a stay of more than 6 hours in the emergency department. However, the difference observed between the groups was mainly related to the emergency room stay component, although the difference remained significant for the risk of hospitalisation considered in isolation. The single-centre nature of the trial, the fact that the composite criterion chosen (emergency room stay) was sensitive to local health conditions, the difference in SARS-CoV-2 seropositivity between the groups at inclusion, the absence of a "true" placebo for some patients (because given orally versus subcutaneously for interferon lambda), and the fact that 60% of patients were treated before the Omicron era raise questions.

It should also be noted that an earlier US phase 2 randomised 1:1 study observed no clinical or virological benefit from interferon lambda (Jagannathan et al. 2021).

All in all, these data do not support the use of interferon lambda as a therapeutic option at present.

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Opinion of the AVATHER group on current therapeutic options (October 2023) for the treatment of early-stage COVID-19

Based on an analysis of the latest available data as at October 2023 :

1) Even if the severity of COVID-19 is less in the Omicron period than with previous variants, the current risks of hospitalisation and mortality, particularly in people at high risk of developing the severe form, justify early treatment for them.

2) This residual seriousness, on the one hand, and the large number of people who need to be treated to avoid an event of interest due to a low overall risk, on the other, justify concentrating efforts on the part of the population most at risk.

3) The very high-risk population most likely to benefit from early treatment of COVID-19 are :

   - solid organ transplants,
   - treated by allogeneic haematopoietic stem cell transplantation,
   - with cancer and haematological malignancies undergoing chemotherapy within the last 12 months,
   - treated with immunosuppressants (including corticoids and anti-CD20)
   - with severe chronic kidney disease (GFR < 30mL/min), including dialysis patients,
   - with chronic poly-pathologies and at least two organ failures,
   - living with HIV with a CD4 count < 200/mm3,
   - suffering from certain rare diseases and at particular risk of infection (Filières de Santé Maladies Rares 2020),
   - with trisomy 21
   - with primary immune deficiency
   - aged > 80 and booster vaccination more than 6 months old

4) People considered to be at high risk should also be able to benefit from early treatment. These people meet <u>at least 2 of the following conditions</u>:

   - COVID vaccination: none or booster more than 6 months old
   - age > 65
   - treated type 1 or 2 diabetes
   - obesity (BMI > 30 kg/m $)^2$
   - respiratory insufficiency from any cause, severe COPD, pulmonary fibrosis
   - chronic renal failure
   - ischaemic heart disease, hypertension and/or heart failure
   - chronic liver disease or cirrhosis
   - history of stroke, dementia, psychiatric disorder
   - severe haemoglobinopathy

5) Nirmatrelvir/ritonavir (Paxlovid®) remains the first-line curative treatment for people with mild to moderate COVID-19, whatever the SARS- CoV-2 variant or sub-variant. It may be a treatment option in patients with severe chronic renal failure (GFR < 30ml/min) and/or haemodialysis, using the most commonly used regimen (300/100mg on D1 then 150/100mg from D2 to D5 as a single dose per day).

6) Treatment with remdesivir (Veklury®) remains the second-line curative treatment when nirmatrelvir/ritonavir (Paxlovid®) cannot be used. It is administered by intravenous infusion and therefore requires day or conventional hospitalisation. It is the preferred option for patients with severe chronic renal failure (GFR < 30ml/min) and/or haemodialysis.

7) The use of sotrovimab (Xeludy®) may still be considered as a third-line treatment as long as XBB variants are in the majority. The group draws the attention of prescribers to the fact that this is a downgraded strategy compared with the two preceding options, due to the lack of clinical efficacy data for the compound on the XBB variants currently in the majority. Recourse to sotrovimab should therefore only be considered in the complete absence of alternatives, and should not be based solely on considerations relating to the current difficulties of access to remdesivir in France (cost and availability). Prescribers must remain particularly vigilant with regard to the risk of resistant mutants emerging under treatment, particularly in immunocompromised patients. Finally, the possibility of using sotrovimab should be reconsidered if the proportion of the BA.2.86 variant increases (beyond a threshold which cannot be precisely defined) due to the loss of *in vitro* activity on the latter.

8) If these 3 solutions cannot be used, the group cannot currently recommend the use of other options outside therapeutic trials, due to the unavailability of the molecules and/or the lack of efficacy data concerning them.

9) Whichever treatment option is chosen, it should be administered as soon as possible after the diagnosis of SARS-CoV-2 infection, ideally within 5 days of the onset of symptoms.

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