Shedding new light on COVID-19 therapeutics during the omicron era: a deeper dive into real-world data

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Ever since the emergence of the SARS-CoV-2 pandemic, the quest for efficacious therapeutic interventions has become a focal point of international health research, focusing on treatment that could avoid disease progression and reduce associated mortality. To this end, three antiviral therapies have surfaced as hopeful prospects: molnupiravir, remdesivir, and nirmatrelvir/ritonavir. These drugs obtained expedited global approval for emergency use following favourable outcomes from randomised clinical trials.[1–3] However, it is worth noting that the demographics of the individuals enrolled in these clinical trials deviate significantly from those requiring such therapies in real-world settings.

Although many manuscripts have been published within the year presenting a range of results, there remains a dearth of adequately powered comparative studies of these treatment modalities.[4–8] The existing literature demonstrates an unequivocal need for rigorous investigations to discern these promising therapies' relative effectiveness and safety. In this regard, the contribution by Torti et al., published in this issue of *The Lancet Regional Health—Europe*, is commendable.[9]

This comprehensive study utilizes data from the Italian Medicines Agency (AIFA) and the National Death Registry to scrutinize an area of research that has previously received less attention. This nationwide prospective cohort study assessed the effectiveness of two oral antiviral treatments, molnupiravir and nirmatrelvir plus ritonavir, in treating non-hospitalised adult patients with confirmed SARS-CoV-2 infections in Italy. The study occurred between February and April 2022, when the country was primarily affected by the BA.1, BA.1.1, and BA.2 Omicron variants. The primary outcome was all-cause mortality 28 days after the initial drug administration. The cohort included 29,553 patients, of which 17,977 were treated with molnupiravir and 11,576 with nirmatrelvir plus ritonavir. After adjusting for variables such as age, comorbidities, and vaccination status, the study found that nirmatrelvir plus ritonavir was associated with a significant reduction in the risk of death compared to molnupiravir. This general finding was confirmed in some subgroups such as females, fully vaccinated patients, those treated within two days of symptom onset, and patients without (haemato)-oncological diseases. The study also reported more adverse events in patients treated with nirmatrelvir plus ritonavir.

An impressive facet of this study is the sheer number of patients examined, thus providing an extensive real-world comparison of the two therapeutic strategies. The treatment cohorts were not identical, as expected in a real-world setting. The users of molnupiravir were generally older and had a distinct comorbidity profile, likely due to the drug's low risk of drug-drug interactions. This inherent variability underscores the need to interpret raw mortality data carefully and encourages a more nuanced understanding of treatment effects.

A striking aspect of this study lies in adopting machine learning algorithms for statistical adjustments, which, although complex, offers an insightful perspective into the effectiveness of these treatment modalities when patient's baseline characteristics are considered. Interestingly, the study's results illustrate a more complex picture than the raw data's initially suggested. Raw data suggest higher mortality among molnupiravir users. However, a contrasting trend appears after the statistical adjustment, suggesting the potentially superior efficacy of nirmatrelvir plus ritonavir in reducing mortality risk. This result holds true even when treatment is initiated early following symptom onset or in fully vaccinated individuals. The findings propose a superior efficacy of nirmatrelvir plus ritonavir in attenuating mortality risk, even when treatment initiation occurs early following symptom onset or in fully vaccinated individuals.

However, assessing the implications and potential limitations of these findings is imperative. While this study serves as a robust benchmark, the unique patient characteristics and healthcare infrastructure in Italy may limit the universal applicability of the results. In addition, the absence of a group of people that did not receive treatment does not permit evaluating these drugs' overall efficacy. Nevertheless, this study presents a compelling platform for further international research, potentially examining the impact of these treatments across different populations and SARS-CoV-2 variants.

Another notable revelation from this study pertains to the significant risk reduction associated with nirmatrelvir plus ritonavir in specific subgroups, such as women, fully vaccinated individuals and those without (haemato)-oncological diseases. This detailed subgroup

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analysis provides a granulated comprehension of treatment effectiveness, paving the way for a more tailored approach to future therapeutic strategies.

In conclusion, the contribution of this research to our understanding of COVID-19 therapeutics during the Omicron era is undeniably substantial. The authors have broadened the scope for future research and enriched the knowledge base that informs clinical decision-making. In addition, data from AIFA could also provide more information on other treatments, such as remdesivir 3-day course, and the efficacy of monoclonal antibodies (casirivimab/imdevimab, sotrovimab, and tixagevimab/cilgavimab), in the different SARS-CoV-2 waves.

Further studies are required to extend and validate these findings across different demographics and viral strains. Nonetheless, this research marks an important step towards an evidence-based approach to treating COVID-19 among high-risk patients, reflecting the ongoing commitment of the scientific community to combat this global health crisis.

Contributors

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Declaration of interests

GM has been advisor for Gilead Sciences, ViiV and MSD and has received speakers' honoraria from Gilead Sciences, ViiV, MSD, and GSK. ADV and AC declare not having conflicts of interest.

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