Gac Sanit. 2026;40(S4):48

Gaceta Sanitaria

https://www.gacetasanitaria.org

230 - TARGET TRIAL EMULATION AND CAUSAL INFERENCE: A USEFUL FRAMEWORK FOR DESIGNING OBSERVATIONAL STUDIES IN CLINICAL RESEARCH

C.M. Rodríguez-Leal, T. Pérez-Pérez, R. Susi-García

Hospital Universitario del Henares, FIIB HUIS HHEN; Facultad de Estudios Estadísticos, Universidad Complutense de Madrid (UCM); Instituto Universitario de Estadística y Ciencia de Datos, UCM.

Resumen

Background/Objectives: Randomized clinical trials are the gold standard for studying causality in medicine, but they are not always feasible due to ethical or economic issues. In such cases, observational studies are the only alternative, but strong assumptions must be made to identify causal effects. These are: no interference, consistency, conditional exchangeability and positivity. The fulfilment of these conditions begins in the study design stage, so investigators must be careful not to violate them. Antiviral treatments for mild SARS-CoV-2 infection were proven in clinical trials for unvaccinated patients. However, they were commercialised for populations with high vaccination rates and different circulating variants to those observed during the clinical trials. Therefore, it was uncertain whether they were effective in preventing progression in vulnerable patients (those with immunosuppression, advanced age, or comorbidities) in such settings.

Methods: To describe the practical implementation of target trial emulation (TTE) framework in Spain to investigate the effectiveness and safety of Nirmatrelvir/ritonavir (NTV/r) and Remdesivir in preventing clinical progression in vulnerable patients with mild COVID-19. The current recommendations regarding causal inference best practices, as well as the results of the COVID-CODE-SPAIN study, are discussed.

Results: The TTE framework was first used in 2008 to reanalyse data on hormone replacement therapy for postmenopausal women. It was formally formulated in 2016. The TARGET Statement, published in 2025, was designed to guide investigators in its implementation. Following these recommendations, the observational data of 2533 patients with mild COVID-19 were analysed. The use of NTV/r was associated with a reduced risk of hospitalization or death from any cause within 30 days, compared to standard of care (SOC): adjusted hazard ratio (aHR) 0.528, 97.5% confidence interval (97.5%CI): 0.330 to 0.845; number needed to treat to avoid one event, 24 (97.5%CI 13 to 283). No difference was detected between remdesivir and SOC: aHR 0.835 (97.5%CI: 0.524 to 1.394). No serious adverse drug reactions were identified.

Conclusions/Recommendations: The TTE framework should be considered when designing observational studies for causal inference. It helps ensure compliance with the four fundamental assumptions necessary for identifying causal effects.

Funding: Project PID2024-155289NB-I00 funded by MICIU/AEI/10.13039/501100011033 and ERDF/EU.

Disclosures: CM Rodríguez-Leal has received speaking fees and funding for conference attendance from Gilead and Pfizer.