Subgroup Mortality Results for Remdesivir in COVID-19: Real or the Play of Chance?

Michael Proschan, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases
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The Adaptive COVID-19 Treatment Trial (ACTT-1) was the first randomized controlled trial showing a beneficial effect of a treatment for COVID-19. Hospitalized patients with COVID-19 randomized to remdesivir plus standard care had a shorter time to recovery and an improved WHO ordinal score at 28 days compared to patients randomized to placebo plus standard care. The secondary endpoint of 28-day mortality showed a non-significant trend for benefit. Subgroup analysis by baseline WHO ordinal score showed no hint of mortality benefit for patients in OS-4 (no oxygen), OS-6 (high-flow oxygen), or OS-7 (invasive mechanical ventilation/ECMO), but an apparently striking effect in OS-5 (supplemental oxygen). We attempt to answer two questions concerning the observed effect in OS-5: (1) Is it real? (2) If it is real, does it reflect an overall effect on mortality or is it a subgroup-specific effect? We illustrate the potential to be misled by multiple comparisons by analogy with a famous controversy outside the field of biostatistics concerning the “Bible code”. Believers, including the great Sir Isaac Newton, posit that a secret code exists in the first five books of the Old Testament that can be revealed only by skipping letters. For example, one might try reading every 50th letter, every 75th letter, and so on until important words and names appear. This Bible code seems to portend historical events such as the rise of Adolph Hitler and the terrorist attack on 9/11/2001, but skeptics argue that seemingly prescient messages are completely consistent with chance.