Evaluate Vantage

April 30, 2020

Remdesivir results pile up, but what do they all mean?

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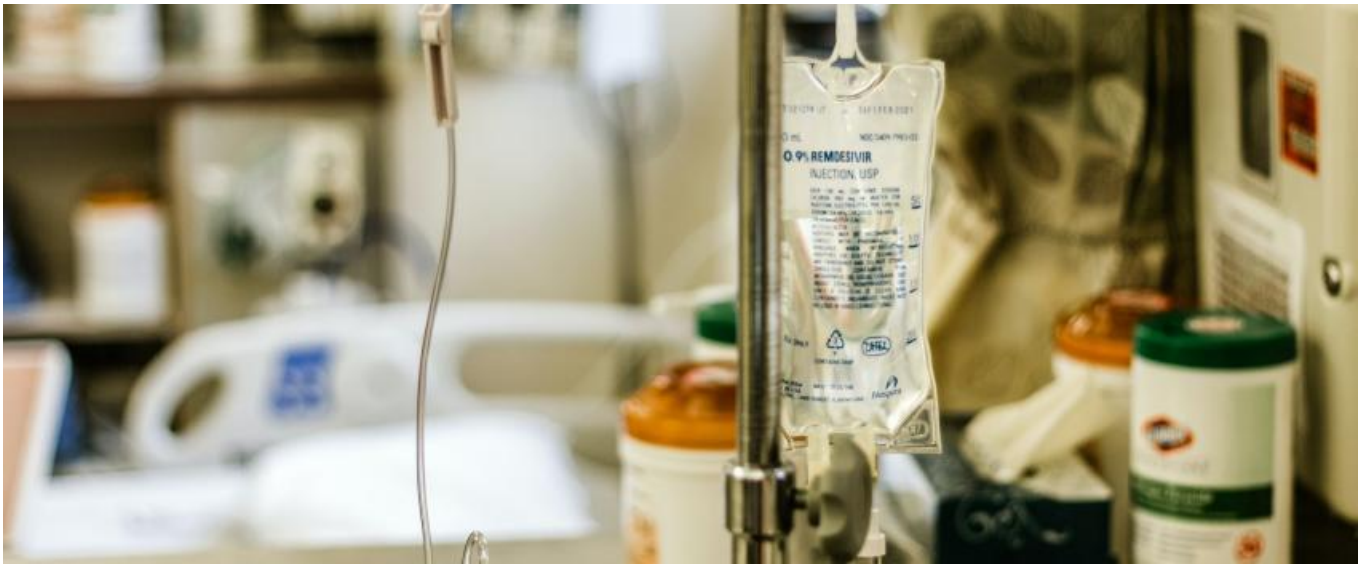

The latest addition to remdesivir's Covid-19 dataset paints a confusing picture, but it's not necessarily bad.

In a market desperate for news of progress against the coronavirus pandemic even highly equivocal results are hailed as a triumph. Gilead's 6% rise yesterday, plus another 3% after close, was down to the dubious result of the NIAID's remdesivir trial as much as the uncontrolled data from the company's own study of this antiviral.

Taken at face value, together with the failed but immature Chinese remdesivir data, Gilead looks to have gone two for three – a bald view that plays down the latest results' shortcomings. But the NIAID and Gilead data are not a failure, either; detailed comparison of the findings does show hints of a benefit, and this could be enough.

For those struggling to keep up with this daily-shifting drama, there are now three remdesivir datasets out, in some form: a Chinese study, rigorously blinded and placebo-controlled but terminated prematurely; Gilead's uncontrolled study; and the NIAID study, which was double-blind and placebo-controlled, but which had an adaptive design that to an extent undermines its findings.

The first reports of remdesivir's activity in Covid-19, revealed separately, concerned compassionate use in 61 hospitalised subjects in a paper published in the NEJM in April; and a leak published in Stat of an internal meeting from a US hospital participating in Gilead's studies. However, neither amounted to anything more than anecdotal case reports from which little definite could be gleaned.

Blinded dataset

This is why formal clinical trial data are important. Those from NIAID's trial, toplined yesterday, showed remdesivir subjects recovering 31% faster than placebo recipients, which was said to be statistically significant. Confusingly, however, this contradicts the China trial, which showed no difference in time to clinical improvement between remdesivir and placebo.

The Chinese study had been powered to show a 15 versus 21-day improvement, and being terminated early is not a wholly convincing reason for its failure: numerically the difference was a highly disappointing 21 versus 23 days.

A crucial consideration when comparing across trials is that recruitment criteria differ. While both studies concerned hospitalised subjects, those in the NIAID trial look like they were less severe overall, something that the relatively better performance of its control arm seems to bear out.

Gilead's own severe Covid-19 study, unveiled yesterday, muddies the waters further since it did not even have a control cohort (*The winds change again for Gilead and remdesivir, April 29, 2020*). And nothing is known about whether subjects' baseline characteristics were balanced across cohorts, either in the Gilead or NIAID trial.

Cross-trial comparisons of remdesivir's three datasets			
	China trial	**Gilead trial**	**NIAID trial**
Trial ID	NCT04257656	NCT04292899	NCT04280705
Enrolment	Halted at 237 (target 453)*	397 (target 6,000)	1,063
Covid-19 severity	Hospitalised, confirmed lung involvement, ≤12 days since illness onset	Hospitalised, severe, ≤4 days since PCR confirmation of disease**	Hospitalised, ≤72 hours (some exceptions) since PCR confirmation of disease
Design	Quadruple-blinded, placebo-controlled	Open-label, uncontrolled, 2-cohort (5-day/10-day)	Double-blinded, placebo-controlled
Primary endpoint	Time to clinical improvement at day 28	Odds ratio for improvement at day 14^	Time to recovery^^
Result	21 days vs 23 days (HR=1.23, not stat sig)	54-65% had ≥2-point improvement	11 days vs 15 days (p<0.001)
Mortality result	14% vs 13% (not stat sig)	8-11% (no control group)	8% vs 12% (not stat sig)
**Terminated early because, China's Covid-19 epidemic having been brought under control, no further eligible patients could be enrolled; **cohort of mechanically ventilated subjects was added in Apr; ^changed from normalisation of fever and oxygen saturation at day 14; ^^changed from disease severity improvement at day 15.*			

Indeed, the only hard (secondary) endpoint common to all three studies is mortality, and crucially none of the three has been able to show a statistically significant improvement, though numerically subjects on remdesivir tend to have a better chance of survival.

Rather, it is tinkering with trial design that could be most revealing: the Gilead study added mechanically ventilated subjects, perhaps because the effect in less severe patients was insufficiently pronounced, while the NIAID primary endpoint was changed from improvement on a scale that included death.

This is not to imply shenanigans, as one study was open-label and the other deliberately had an adaptive design. But the hints are that remdesivir might not, after all, have a major impact on preventing the death of people infected with Covid-19.

However, the fact that this is not on the cards need not spell disaster, and perhaps investors are right in not looking for a home run. At this stage of the pandemic, when some countries' hospitals risk being overwhelmed by patient numbers, a drug that merely reduces the severity of disease could make a real difference.

Remdesivir might, just about, be capable of that.