Evaluate Vantage

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For severe Covid-19 pin your hopes on antibodies

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Failure of BTK inhibition puts the pressure on Lilly, Regeneron and Astrazeneca to deliver with antibodies to treat severe Covid-19.

The pressure on antibodies to provide the answer to treating Covid-19 just moved up a notch. This is because Astrazeneca's Calquence has failed in hospitalised patients, a development that puts a question mark over the idea that a BTK inhibitor could reduce the coronavirus's severest symptoms.

This follows disappointment with another symptomatic approach, IL-6 blockade, which has seen studies of Roche's Actemra and Sanofi's Kevzara disappoint. If Calquence shows that BTK inhibition is a non-starter then investors should not expect much from ongoing trials of Abbvie/J&J's Imbruvica or Sorrento's abivertinib either.

If the theory behind hitting IL-6 – that surges in cytokines cause coronavirus patients to become severely ill – was nebulous then the one underlying the BTK approach was related though even more uncertain. BTK has numerous effects and regulates the production of cytokines including IL-6, and if an elevation in these lay behind respiratory complications then inhibiting BTK might have been a solution.

However, the actual involvement of cytokine production in Covid-19 is now thought to be much more complex, and certainly the elevations are not as high as in, say, patients on Car-T therapy suffering so-called cytokine storm.

No Calavi joy

This morning Astra said the Calavi programme of 224 hospitalised Covid-19 patients had failed to show that Calquence on top of standard of care cut mortality or respiratory failure, its primary endpoint, versus standard care alone.

An earlier scientific publication had suggested that Calquence reduced markers of inflammation and improved clinical outcomes in severe Covid-19 disease. Calavi is split across two separate clinicaltrials.gov entries, for US and ex-US patients, and interestingly the former's primary endpoint was measured at 28 days, while the latter's was at 14.

At least two other BTK inhibitors are in the clinic: Imbruvica and abivertinib. Sorrento licensed the latter, which hits EGFR as well as BTK, from Acea Therapeutics in May, and two phase II trials in Covid-19 are getting under way.

The NIAID has just started enrolment into Respond, a study of unspecified BTK inhibitors that will assign 120 patients to three groups: those without Covid-19 on BTK inhibition for other reasons, and those with Covid-19, who will either get a BTK inhibitor or not.

This could demonstrate more precisely whether BTK plays a role in coronavirus-related inflammation, but those looking at the Calquence trials might say they already know the answer.

Selected trials of symptomatic Covid-19 drugs in hospitalised patients			
Product	**Company**	**Trial**	**Key primary endpoint**
BTK inhibitors			
Calquence	Astrazeneca	Calavi US	28-day mortality or respiratory failure (failed)
		Calavi	14-day mortality or respiratory failure (failed)
Abivertinib	Sorrento (ex Acea)	NCT04528667	29-day hospital discharge
		NCT04440007	14-day mortality or respiratory failure
Imbruvica	Abbvie/J&J	NCT04439006	Reduction in respiratory failure & death
Anti-IL-6 MAbs			
Actemra	Roche	Covacta	28-day improvement on 7-point ordinal scale (failed)
		Empacta	28-day reduction in requiring ventilation (succeeded)
Kevzara	Sanofi/Regeneron	NCT04327388	Time to 2-point improvement in 7-point ordinal scale (failed)
Sylvant	Eusa Pharma	Silvar	28-day mortality
Levilimab	Biocad	Corona	14-day clinical recovery
Sirukumab	J&J	NCT04380961	Time to 2-point improvement in 6-point ordinal scale
Olokizumab	UCB/R-Pharm	NCT04380519	15-day 1-point improvement in 6-point ordinal scale
Source: clinicaltrials.gov & company reports.			

Earlier, the IL-6 blocking approach was dealt blows when Sanofi/Regeneron's Kevzara failed to yield an improvement in Covid-19 patients on ventilators, and Roche's Actemra flunked the Covacta study in hospitalised patients with severe Covid-19-associated pneumonia.

However, Roche's Empacta study, also in hospitalised patients with Covid-19 pneumonia, was later said to have succeeded. However, the statistical effect was not overwhelming, with the upper bound of the confidence interval for risk of death or mechanical ventilation only just below 1.00.

Another arguable bright spot for Covid-19 symptom treatment came with yet another approach said to control cytokine release, Jak inhibition, when Incyte/Lilly's Olumiant showed an effect on recovery time in the ACCT-2 trial; however, there was no significant improvement in survival. Incyte/Novartis plan to reveal results of Jakafi's phase III Ruxcovid trial by the year end.