Notes on COVID-19

Part 24: 2021-03-01 to 2021-03-24

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2021-03-23 Nature reported on 2021-03-12 on two antibody therapies for mild to moderate Covid-19 that seem to inhibit the development of severe disease https://www.nature.com/articles/d41586-021-00650-7 The trials were randomised, placebo-controlled and double-blind.

One is developed by VIR Technologies of San Francisco and GSK (Glaxo Smith Kline). A report on the efficacy of monoclonal antibodies VIR-7831 with VIR-7832 in treating mild to moderate Covid-19 is in preprint at bioRXiv: The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2, Cathcart AL, Havenar-Daughton C, et al https://www.biorxiv.org/content/10.1101/2021.03.09.434607v1 2021-03-10. The combination therapy was found to reduce the risk of hospitalisation and death by 85%.

The other report concerns the Eli Lilly nonclonal antibodies bamlanivimab and etesevimab. The combination reduced the risk of hospitalisation and death by 87%.

The drugs are already authorised for use in the US. The question is why uptake has been so low. One reason may be that these are treatments for mild to moderate disease. They are given by infusion, which means in a hospital or specialist outpatient clinic, and the logistics of doing so when hospital facilities are already overstretched with seriously-ill patients are daunting. You need to provide for people who would otherwise be at home, and it is the case that there are far more people who contract and recover from mild disease than progress onto severe disease, so there would be potentially huge numbers of potential takers. Something like the British Nightingale hospitals might have been appropriate, but they are gone too now.

It should also be noted that these studies are relatively small. Whether they would scale up to large-scale therapies is still open. Also, the Eli Lilly drugs have been reported on before, in trials on hospitalised patients with more severe disease, and were found not to affect the course of severe disease very much, so it may be that medical people lost interest in them, because the "big thing" so far has been how to deal with severe disease.

2021-03-23 Last week, on Monday 2021-03-15, Germany stopped vaccinating people with AZD1222 (now apparently known as COVID-19 Vaccine AstraZeneca), because of occurrence of some cases of cerebral sinus vein thrombosis (CSVT) along with thrombocytopenia within some time after vaccination (a few days – 14 days). This had happened in Austria, as well as Denmark and Iceland, and they had also stopped AZD1222 vaccination until the situation was clarified.

The occurrence was very unusual. The Paul Ehrlich Institute, the German agency responsible for

vaccines, had said on Monday 15th that there were 7 “new” cases. Health Minister Spahn said that there had been 1.6m vaccinations in Germany with COVID-19 Vaccine AsstraZeneca. (Report in German at https://www.deutsche-apotheker-zeitung.de/news/artikel/2021/03/15/deutschland-setzt-impfungen-mit-astrazeneca-vorsorglich-aus). The German government asked the EMA to investigate and assess the situation. The head of the EMA, Emer Cooke, said on Tuesday 2021-03-16 that the agency was firmly convinced that the benefits of continued vaccination with the AstraZeneca vaccine outweighed the risks https://www.theguardian.com/world/2021/mar/16/benefits-of-astrazeneca-jab-outweigh-risks-says-eu-regulator An EMA report was expected Thursday 2021-03-18 and duly came, saying that, along with the recommendation that recipients be informed of the few cases of cerebral thrombosis that had occurred (it is part of a requirement anyway in Europe that recipients of a medicine be informed of possible side effects).

Karl Lauterbach, the member of the German parliament for Leverkusen/Cologne-Müllheim and the health spokesman for the minority coalition partner SPD, as well as being a doctor and Professor of Health Economy and Clinical Epidemiology at the University of Cologne and an Adjunct Professor of Health Policy and Management at the Harvard School of Public Health, and a well respected commentator on matters medical, cricitised the decision to stop vaccinating, on the basis that the benefits of continuing vastly outweighed the risks. He is surely right. Many thousands of people were not vaccinated at the appointed time and will therefore remain susceptible to Covid-19 for longer. Also, vaccine already prepared for injection will have been thrown away. A more appropriate political reaction to the events might have been to anticipate what the EMA was going to recommend and ask people specifically if they were willing to risk being vaccinated, given these rare occurrences.

An eight case arose on Tuesday March 16th, and then five more became known up to Thursday 2021-03-18 (https://www.pharmazeutische-zeitung.de/bekannte-fallzahl-steigt-auf-13-124456/ , in German). So actually there has been a cluster of 13 German cases in 1.6 million vaccinations. That is more than the 1 in a million occurrence often considered to be “background” risk (Lewis HL, Technological Risk, W.W. Norton & Co., 1990). But Astrazeneca pointed out there have been world-wide some 17m recipients of their vaccine, so in fact the worldwide figures (when you add in the few cases in other countries) do come out close to 1 case in a million.

So what is known?

A research professor at the University of Greifswald, Andreas Greinacher, is an expert in a rare illness which has characteristics in common, namely Heparin-induced Thrombocytopenia (HIT). The common blood-thinner heparin, used ubiquitously before medical operations in which the patient might be at risk of thrombosis, has led in rare cases to clotting and thrombocytopenia (a deficit of white platelets). A review article is Greinacher A, Althaus K, Krauel K, Selleng S, Heparin-induced thrombocytopenia, Hamostasiologie 2010 Jan;30(1):17-8, 20-8 (indexed in PubMed at https://pubmed.ncbi.nlm.nih.gov/20162249/ which also points to more articles by Greinacher and others), and another in the N. Eng. J. Med (paywall), Greinacher A, Heparin-Induced Thrombocytopenia, 2015-06-15, N Engl J Med 2015; 373:252-261, DOI:

10.1056/NEJMcp1411910 https://www.nejm.org/doi/full/10.1056/NEJMcp1411910 . Professor Greinacher contacted the Austrian authorities and the PEI, to obtain blood samples from the CSVT patients after AZD1222 vaccination, and said on Friday that they had found antibodies which worked to induce the thrombosis and thrombocytopenia. An autoimmune reaction with considerable similarity with HIT https://www.spiegel.de/wissenschaft/medizin/astrazeneca-greifswalder-forscher-haben-offenbar-ursache-fuer-thrombosen-gefunden-a-315f84ce-7020-47da-935f-b3594ec1446d (in German but Google will translate accurately for you). Apparently it occurs in HIT 5-14 days after heparin injection, and a similar timeframe is found in the CSVT patients after COVID-19 Vaccine AstraZeneca injection.

There are two pieces of good news associated with this. First is that there are specific symptoms, namely painful leg (an indication of thrombosis) or headaches persisting for a number of days after injection (headaches are common side-effects of COVID-19 Vaccine AstraZeneca injection, but short-lasting and only during some 10-24 hours after injection). So, if you have those symptoms, visit your doctor urgently. Second, there is an effective therapy (for symptomatic people, unfortunately not prophylactic), namely a high intravenous dose of immunoglobin (Ig).

Why this information has not made it into the English-language news media is puzzling to me. I did send a tweet to TheG Live blog when the information came out on 2021-03-19, so it is not as if they don't know.

2021-03-23 On Monday, 2021-03-22, AstraZeneca reported that it has completed its US Phase 3 trial of AZD1222, which included a significant cohort of older recipients https://www.astrazeneca.com/media-centre/press-releases/2021/astrazeneca-us-vaccine-trial-met-primary-endpoint.html It was 79% effective at preventing symptomatic Covid-19, 80% in the over-65's, and 100% effective at preventing hospitalisation and death.

The trial enrolled some 32,000 participants, https://www.theguardian.com/society/2021/mar/22/astrazeneca-covid-vaccine-79-effective-with-no-increased-blood-clot-risk-us-trial . TheG article says “no added risk of blood clots”. This is unsurprising. In 32,000 participants, the chances were only around one in thirty that they would have a single case. But this announcement will have reassured some people.

2021-03-23 BBC Panorama's Jane Corbin summarises on 2021-03-22 the public-health measures which have proven effective in some places in containing the damage from Covid-19. Nothing we didn't know; just clearly and succinctly stated, with concrete evidence https://www.bbc.com/news/uk-56455030 . Thanks to Nature Briefing (Springer Nature's daily emailing) for the pointer.

2021-03-24 Pfizer has started a Phase 1 trial of an antiviral against Covid-19. It is designated PF-07321332 and is a protease inhibitor. They correctly say in their press release that therapies are part of a necessary two-pronged strategy for countering Covid-19, the other prong being vaccination https://www.pfizer.com/news/press-release/press-release-detail/pfizer-initiates-phase-1-study-novel-oral-antiviral

2021-03-24 Kaleido Biosciences has had a therapeutic drug KB109 for mild-to-moderate in trial for some time, and has today announced good results for both inhibiting progression to severe disease and reducing the duration of the illness. To date, I have found only the following announcement https://www.nasdaq.com/articles/kaleido%3A-kb109-shows-favorable-safety-tolerability-profile-in-non-ind-study-2021-03-24 Kaleiido Biosciences did announce "positive" preliminary results in January, on which there is more info https://www.microbiometimes.com/kaleido-biosciences-announces-positive-interim-results-of-controlled-study-of-kb109-in-patients-with-mild-to-moderate-covid-19/ The interesting part about KB109 is that it is Microbiome Metabolic Therapy, that is, it acts on the microbiome in your gut. It was involved in one trial, called VITORA, registered with clinicaltrials.gov in the US https://clinicaltrials.gov/ct2/show/NCT03944369 , where KB109 is described as a glycan https://en.wikipedia.org/wiki/Glycan . The current trial seems to be open-label and may be this one: https://clinicaltrials.gov/ct2/show/NCT04486482

2021-03-24 It is getting hard to avoid commenting on the politics behind the EU's sluggish roll-out of vaccines, and Germany's in particular. There are hints that there are quantities of unused COVID-19 Vaccine AstraZeneca lying around waiting to be used, at the same time as the EU is quibbling with AstraZeneca that it is not delivering enough. If so, this is a silly and dangerous muddle. The EU is apparently weighing a "vaccine export ban", that is, requiring all vaccines produced in the EU to be used in the EU. Irish Taoiseach Micheál Martin is very much against it, calling such a step "retrograde". He pointed out that BNT162b2, for example, is made from material from 86 suppliers in 19 countries https://www.irishtimes.com/news/politics/absolutely-vital-to-keep-vaccine-supply-chains-open-martin-says-1.4516787 It is hard to disagree with Martin's assessment. When somebody stops companies shipping completed vaccines, others may stop shipping ingredients, and then production is set back, which is surely the last thing anyone wants when there is a shortage! The Brussels-based journalist Leo Cendrowicz has a level-headed comment in TheG today https://www.theguardian.com/commentisfree/2021/mar/25/an-eu-ban-on-vaccine-exports-would-make-its-wretched-rollout-take-longer-still