Cancerworld

Treatment of COVID complications

Adriana Albini / 17 April 2023

As we have seen in the last 20 months, SARS-CoV-2 has evolved. .
SARS-CoV-2 has consistently mutated over the course of the pandemic, resulting in variants that are different from the initial SARS-CoV-2 virus. Covid disease has changed as a consequence of mutations in the genetic code occurring during viral replication and so have the issues of variants and immunisation, which now has covered the vast majority of the Western world. Especially with Omicron, we went through a huge wave of spontaneous infection and natural immunisation. The issue of Covid is still crucial and it primarily concerns the vulnerable population, people suffering from a series of diseases including cancer and a variety of malignancies. Three specialists discussed these themes in the second online seminar, part of the SPCC project "Cancer & Covid: Prevention and Treatment including Monoclonal Antibodies (MoABs)", which took place on 8 March 2023, and was chaired by **Giovanni Di Perri**, Professor of Infectious Diseases at the University of Turin, Italy, and Head of the Department of Clinical Infectious Diseases.

Covid and lung cancer patients: focus on the effects of treatment

Alfredo Addeo is Consultant Medical Oncologist at the University Hospital of Geneva, Switzerland. Although we may feel that the pandemic is no longer affecting us today, it is crucial to understand where we began and where we are now, especially regarding patients with lung cancer and, in general, patients with active cancer, who have been affected by COVID-19 perhaps more than the

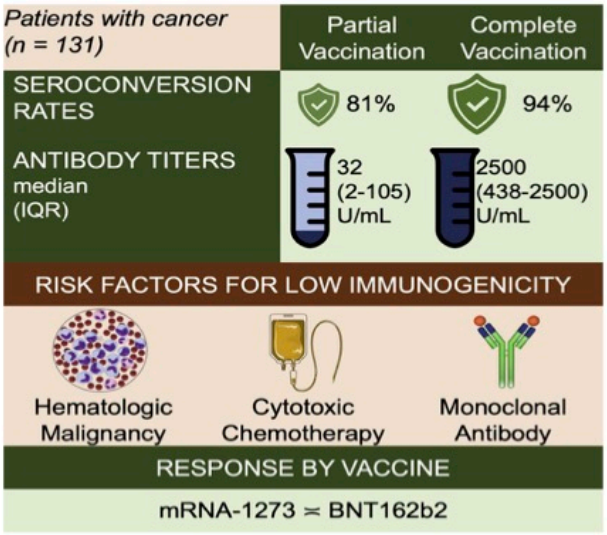
rest of the population. When the pandemic hit, we started asking ourselves questions such as whether patients with cancer were at increased risk of getting SARS-CoV-2 infection. Are patients with cancer more vulnerable to the virus? Does anti-cancer therapy affect COVID-19 outcomes? At the beginning, looking at cases from China, the general impression among clinicians was that patients with cancer were somehow more exposed. However, there were other important risk factors, such as smoking, comorbidities, age, etc. Naturally, cancer patients tend to be aged. So, potentially, they could have been more affected by the virus for reasons other than their cancer or cancer type. Still, it seemed that patients with any form of cancer had an increased risk of getting this infection. This was pretty much all the information at our disposal in the early months of 2020. What about **vulnerability**? The initial data we had from real-time registries, with all the intrinsic limitations of registries, seemed to indicate that the fatality rate was quite high, perhaps even up to 41%. The information we garnered was that people with cancer had a higher risk of developing Covid, of experiencing a severe course and perhaps even dying. The cancer community decided to collect the data as best as they could: the CCC-19 was created for this purpose, and produced a US pan-cancer analysis. There was also some initiative specific to thoracic malignancies, a study called TERAVOLT, where fatality rates seemed to be almost double those in the CCC-19 registry. TERAVOLT is itself a registry and, as such, many data might be missing. Still, this is the kind of information we had in 2020. How about **cancer therapy**? If we administered chemotherapy, could it make the infection worse? Does chemo have an impact? How about the immune checkpoint inhibitors, which are part of the treatment? And targeted therapy? Information was scattered at best, but we assumed that, because chemotherapy can cause neutropenia, the immune system of patients under this therapy may have been at higher risk of getting infected and also of developing a severe manifestation of COVID-19. Even for this the data was coming from different registries. There was OnCOVID, specifically for cancer. Also in this case, the impression was that a patient who is on chemotherapy might be at higher risk. Then an important study was published on Lancet in May 2020. It was conducted by the UK Coronavirus Cancer Monitoring Project, and it did not seem to point in the direction that patients with cancer may have a higher risk, necessarily. It very much appeared to depend on the fact that we are considering a population that has other comorbidities. It is also normally an aged population. The only thing that seemed to have a particular role was chemotherapy treatment, but, again, no strong correlation emerged from this study.

Moving forward, YEAR 2021

Then came 2021. We were looking for a vaccine and were eager to offer it to patients with cancer, to make sure they were protected. Those patients were fragile because of the illness, of the treatment, the age, and comorbidities. A recommendation went out as soon as the mRNA and other vaccines were released, that patients with cancer should be vaccinated. Of course, patients on active treatment with cancer were not necessarily in the study that led to the approval of that vaccination. Still, oncologists thought it was important to expose their patients as soon as possible. At that point more questions arose: What is the efficacy in this population? What is the safety? Do anticancer treatments affect its safety/efficacy? We had enough data to know the vaccine was safe per se, and a lot of literature had been published on cancer and Covid by this point. Data presented at ESMO 2021 on the activity of the vaccine in cancer patients indicated that it was indeed very safe. We should not forget where we were at in 2021 after a very difficult year, we did not know exactly what to expect.

Dr Addeo and his team participated in a study, together with the MD Anderson Cancer Center, that was published in Cancer Cell in August 2021. They recruited patients with haematological and solid cancer, and then exposed them to the vaccination. At that time, vaccines were administered in two doses, and the team tried to measure their efficacy. The only way they had to do that, which is very criticisable, was to see whether there was any antibody titers response. They saw that for solid tumours, irrespective of the treatment given, there was some immune response. The only case where they did not see any reactivity was in patients with haematological diseases, particularly those exposed to rituximab. This had been shown in other studies as well, and was confirmed by the VOICE trial which came out soon after, and was conducted along very similar lines. The research indicated that in the case of a solid cancer, it did not make any difference whether the patient was receiving chemotherapy, immunotherapy, or chemoimmunotherapy treatment, the only drugs that seemed to affect the immune response were immunosuppressive drugs or drugs like rituximab and CD4. So, to summarise the data that was available: the only way we had to measure this was the number of incidents of the infection and the measuring of the immune response. We obviously couldn't run a study and we were confident that the vaccines were safe and effective in terms of inducing an immune response for the vast majority of patients, with few exceptions, particularly for haematological diseases.

Immunogenicity of SARS-CoV-2 messenger RNA vaccines in patients with cancer
Alfredo Addeo, et al, Cancer Cell Volume 39 Issue 8 Pages 1091-1098.e2 (August 2021)
DOI: 10.1016/j.ccell.2021.06.009



What has been the impact of Covid on the cancer pathway? We know that unfortunately for two years we have focussed on the pandemic and partly overlooked cancer, particularly the new cases, as the standard pathway was disrupted and there were patients who had not been diagnosed with cancer. It is not true that after the vaccine we are seeing an increased number of cancer cases. The reason is that we did not diagnose cancer enough in 2020-2021 because some of the regular screenings were stopped. We were not investigating people as we usually do, and so, there is a backlog of patients who are getting diagnosed with cancer only now. This is not just in Italy, but in other countries as well, there was a clear dip in the number of cases diagnosed over the Covid years. The take home message is that vaccines are safe for patients with cancer and on treatment. Covid had a huge impact on cancer pathways and on management, and we should not forget that vaccines helped us get out of the pandemic earlier.

Drugs approved by the EMA: indications and limitations

Marco Cavaleri is Head of the Office of Biological Health Threats and Vaccine Strategy at the European Medicines Agency (EMA), and Co-chair of the EMA COVID-19 task force. Dr Cavaleri opened his presentation with a snapshot of the drugs approved by the EMA. There are two monoclonal antibodies products approved for prophylaxis. One is the cocktail composed of **casirivimab/indevimab** from Regeneron. The other is **tixagevimab/cilgavimab** from AstraZeneca, which is called Evusheld. Then there are four monoclonal antibodies and two antivirals approved for treatment of outpatients with mild COVID-19 but at higher risk of progression. As we know from clinical trials and in general from antivirals in acute viral diseases, starting to take this type of medicines as soon as possible is crucial to obtain real benefits. **Remdesivir** was the first antiviral to be approved. The EMA gave it a conditional market authorisation already in the first half of 2020, and it is the only one that is also approved for the treatment of hypoxic patients with more severe COVID, hence already hospitalised. This is probably due to the fact that at that point in time there were still clear effects of antivirals in patients hospitalised with more severe COVID-19, while now, with the Omicron variant, it is extremely difficult for any antiviral to demonstrate a profound effect once a patient is progressing to more severe disease. Remdesivir had been studied before for other viral diseases, such as Ebola, and was easily repurposed to COVID-19, because there was already a lot of knowledge, at least in terms of preclinical toxicity, dosing, pharmacokinetics, and safety in humans. Then we have the combination of **nirmatrelvir/ritonavir**, known as Paxlovid. It is a protease inhibitor and probably one of the best drugs currently available for this type of use. Ritonavir is an antiretroviral given in combination to the active substance nirmatrelvir to boost its effects. There are also some monoclonal antibodies, including two cocktails, **casirivimab/indevimab** and **tixagevimab/cilgavimab** that are also approved for prophylaxis. Then we have **sotrovimab**, sold under the name of Xevudy, and **regdanvimab**, which has not been widely adopted, at least in Europe. Finally, we come to products that are used in a later phase of the disease, the so-called **immuno-modulators**. The EMA has been able to approve only three of them: **tocilizumab, anakinra** and **dexamethasone**, even if the latter was mainly approved by centralised procedures, because the majority of dexamethasone products were already approved nationally, so there was no need for the EMA to intervene. There are other products that have been through the late-stage clinical trials and the EMA will be eagerly looking into all of this additional evidence and try to expand the armamentarium, if possible.

There are a number of products approved as antivirals, monoclonal or small molecule, and we could be in a good position overall. Unfortunately, particularly with monoclonal antibodies, they were most effective in clinical trials when they were able to neutralise the variants in circulation. But with the new variants, in particular the Omicron descendants, the landscape has changed dramatically. Looking at the results of a study published in the *New England Journal of Medicine* on January this year, we see that the actual ability of different monoclonal antibodies in vitro to neutralise the

Omicron XBB subvariants is low or non-existent. Even increasing the dose, the neutralisation is below 20, 30%, which is practically nil. The EMA has issued a warning on the use of these monoclonals for treatment or prophylaxis. **Bebtelovimab** is a monoclonal antibody that received an emergency authorisation by the FDA in the US, but was never approved in Europe, mainly because the company had just enough supplies for the United States. There was an interest to bring this product to Europe, as it seemed to be coping better with Omicron 2 and 5 than other monoclonal antibody products, but it is actually doing quite poorly against BQ.1.1, and with XBB it is completely flat. Today it is very difficult to consider any of those drugs that were approved as an option for patients in need. On the other hand, small-molecule antivirals have a different mechanism of action. They do not target the spike protein, which changes so much, they have more conserved targets instead, and a more conserved mechanism of action. **Remdesivir, nirmatrelvir** and also **molnupiravir** are retaining their in vitro activity against all the current subvariants, so they remain a good option. These small molecules can be taken in their indication for use, which is treatment of mild COVID-19 in order to prevent progression. But they are not approved for prophylaxis, which is a major problem, for instance for patients that are immunocompromised, particularly those who are not responding to vaccination. Some subpopulations are still not seroconverting or showing high levels of B-cell or T-cell responses even after receiving four or five doses. **Paxlovid**, which is **nirmatrelvir-ritonavir**, seems to be the first choice in this case, it has shown to work well in a randomised clinical trial that was conducted before the spread of the new Omicron subvariants, and also from real-world evidence data. A study from Colorado, in the US, at a time when Omicron 4 and 5 were dominant, shows clearly the efficacy of this product, including in a number of very vulnerable patients, such as the immunocompromised. It is reassuring to know that this product remains a very good option. The major problem with Paxlovid is that it has drug-drug interaction, so in many cases it has to be used very carefully, and can even be contraindicated, and in those cases where co-medication cannot be stopped, this product should be avoided.

Another antiviral that has garnered significant attention, but for which the EMA has not been able to give a positive opinion, is molnupiravir. It is one of the small-molecule drugs that could be extremely helpful in patients with potential drug-drug interaction or other safety aspects precluding the use of other products. The problem with molnupiravir is that the pivotal study conducted by the company did not give strong evidence of efficacy and was not meeting the EMA's regulatory standard. The agency was also waiting for the results of the PANORAMIC study, a very large randomised clinical trial conducted in the United Kingdom. More than 20,000 patients were recruited. Unfortunately, it was open-label, so the data on time to resolution of symptoms was not available, but in terms of the primary outcome, i.e., progression to hospitalisation and severe COVID-19, there was no difference between molnupiravir and no antiviral. An important factor here is that in the context of Omicron, the progression to severe disease is much lower than in the previous waves, like Delta, for example. When the clinical trials were conducted during Alpha and Delta, progression to severe disease in the placebo arm was 10% or even 15% in some studies, while now it is less than 1%. So, it is much more difficult today to establish what an antiviral can achieve using this important clinical endpoint. This is the intrinsic problem with molnupiravir, and the European regulators are trying to figure out a way to design clinical trials that can demonstrate the efficacy of new antivirals. A large real-world-evidence study, from approximately 6,000 patients, was conducted in the UK with the OpenSAFELY platform at the time when Delta and Omicron 1 were predominant. The results indicated that sotrovimab was performing much better than molnupiravir in terms of preventing progression to severe disease. Looking at the subgroup analyses, including solid cancer, haematological disease, renal disease and immunosuppression, we see that this is very much consistent across the board. We know that molnupiravir is active in humans as an antiviral, but is not the most potent. So, particularly in the immunocompromised population, we need to be cautious with its use. Moreover, due to its mechanism of action, it might be responsible for a huge amount of mutation in the virus, which so far is not translating into anything worrisome, but many virologists are extremely

concerned about such behaviour. This is something we need to watch out for in the future.

Sotrovimab has also been the subject of considerable discussion because, unlike other monoclonal antibodies, it does not act purely by neutralising the virus. It has other properties as well, including ADCC or antibody-dependent cellular cytotoxicity. It is important that we take into account this other pharmacological activity when we look into the efficacy of the drug. A study conducted in Amsterdam showed that even for strains for which naturalisation is pretty poor with sotrovimab, such as Omicron 2, there is a component of ADCC, and in animals there was quite a good protection from replication of the virus in the lungs. It is important to factor in this aspect, but the problem is that we do not have the metrics to do that. Assessing the significance of this supplementary pharmacological activity on the effectiveness of sotrovimab is highly challenging, particularly given the poor neutralisation of the monoclonal antibody against the new subvariants. A study conducted when Omicron 1 was predominant demonstrated that in immunocompromised patients there was a proclivity towards the emergence of variants that exhibit resistance to sotrovimab. There were many patients in which viral loads more than 106 were not uncommon when treated with sotrovimab. Now that XBB and other subvariants of Omicron are spreading, we have to be extremely cautious to use a monoclonal antibody like this one because it might not be for the good of the patients.

As for **immunomodulators**, among those that are approved is **anakinra**, sold under the brand name Kineret. This is an interesting immunomodulator that acts on the interleukin receptor, at the starting point of the cascade of inflammation. The programme, that was conducted by academic groups, not by the company, aimed at selecting patients according to a biomarker often used in ICU as a marker of inflammation, called suPAR, which stands for Soluble Urokinase Plasminogen Activator Receptor. A phase II study demonstrated that these patients have a poor prognosis and a higher risk of progressing to severe disease and mortality. A phase III trial was then conducted using essentially the same design, which demonstrated a profound impact of this drug compared to standard of care according to the classical WHO clinical progression ordinal scale by day-28. Also, mortality was extremely significant as an endpoint, demonstrating the efficacy of this product, which was approved. Unfortunately this biomarker is not available in many parts of Europe and this, of course, could be a problem for using the drug in clinical practice. The other product that the EMA has approved is **tocilizumab**. It went through a somewhat tortuous journey, because a number of studies had been carried out before a big recovery randomised clinical study was conducted by Oxford University in the UK with a large dataset of 4,000 patients, comparing tocilizumab to usual care. It was a secondary randomisation with patients with high-level of CRP; nevertheless they were able to demonstrate a 4% reduction in the 20-day mortality rate. The concomitant use of corticosteroids was a key aspect. The EMA approved this product to be used in combination with corticosteroids because without them there is no sufficient efficacy demonstrated so far. Meta-analyses with a number of studies conducted with this drug overall indicated some effect on mortality.

What is next? Next-generation monoclonal antibodies that might be active against Omicron subvariants, or with more conserved epitopes, are being discussed. A new pathway based on the immunobridging of ex vivo neutralising antibodies has been developed, in order to allow a faster approval of new monoclonals capable of tackling the variants that are circulating at that specific moment, instead of always falling behind of the virus's mutations. Other antivirals are warranted, especially oral agents with less drug interactions. Sotrovimab and other antivirals could possibly expand the armamentarium of small molecules. New products under development for patients with severe COVID and ARDS, such as **sabizabulin** and **vilobelimab** have shown promising data. Lastly, it is very important to think about different treatment strategies based on the combination or sequential use of different immunomodulators, maybe also with some antivirals, in selective patient phenotypes. Ultimately, we still need to better define what kind of patient could benefit from a

certain type of immunomodulator agent, what type of combination, and in which stage of their disease and progression they would get the biggest impact.

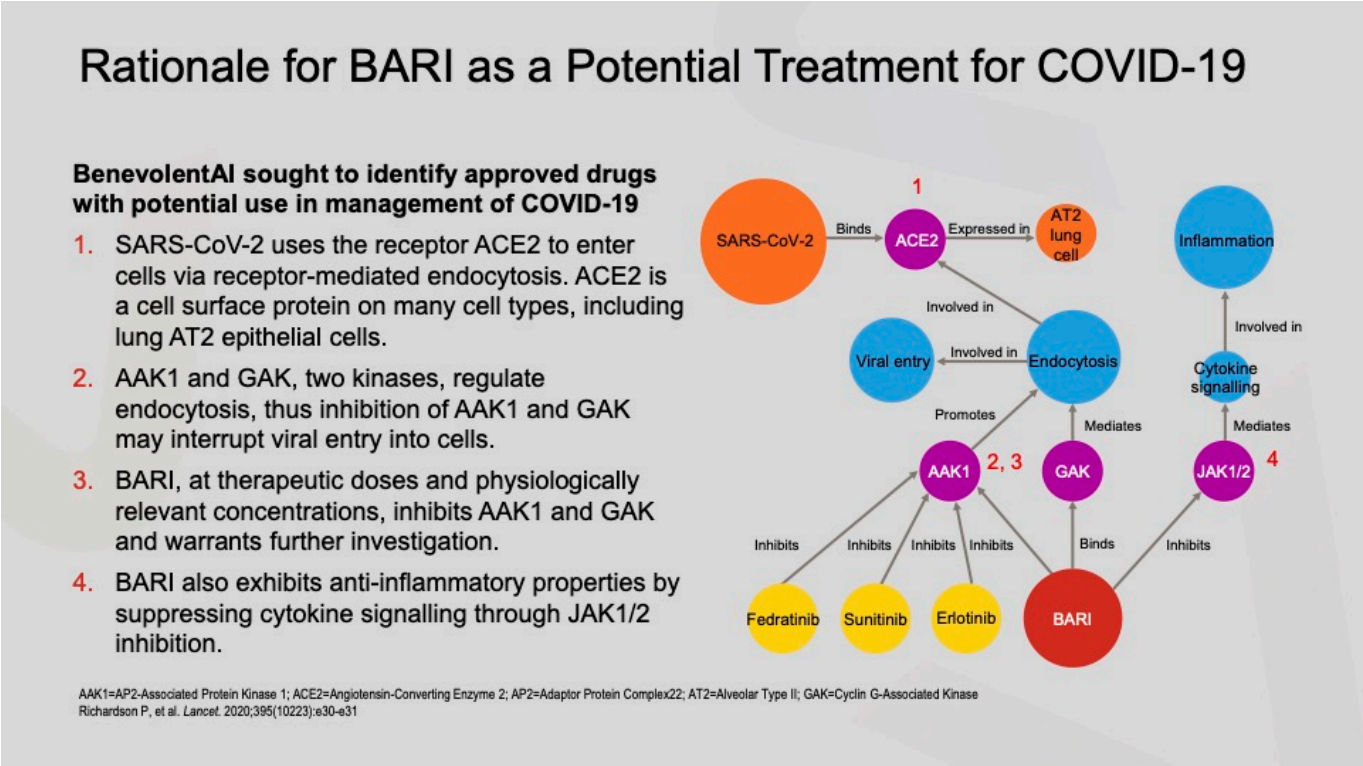
From Al to regulatory approval in 9 months: the pandemic baricitinib story

Justin Stebbing is Professor of Biomedical Sciences at ARU, Cambridge, Editor-in-Chief at Oncogene and Visiting Professor of Oncology at Imperial College London, UK. Right at the start of the pandemic, Prof. Stebbing sat down with a team from BenevolentAI, a small company in London he was working with. This was January 2020, and Europe was becoming increasingly worried. The team asked the artificial intelligence if there was an existing drug that could help with the pandemic. They used the 2 billion parameters in the natural language processing algorithms to identify that Lilly's drug **baricitinib** could be very useful. It was no surprise that a medication for rheumatoid arthritis might affect people with cytokine release syndrome, but what was really interesting is that the team used the knowledge graph to ask a slightly different question, which was not only if it would affect the cytokine release syndrome, but if it could affect unintended human targets and induce antiviral effects. The answer was that baricitinib would not only have a role in the ARDS caused by abnormal cytokines, but would actually affect viral entry by inhibition of two host kinases, AAK1 and GAK, needed by the virus for endocytosis. That was indeed very interesting, but it was only a computer prediction. After publishing these results in the Lancet, many colleagues from Italy, and Milan in particular, that Prof. Stebbing had worked with two decades earlier on Kaposi sarcoma, contacted him, as they were becoming increasingly overwhelmed. All there was available at that point was a computer-predicted dual mechanism. All they knew was that the viral entry mediated by ACE2, which had recently been identified as a receptor, could be impacted, as well as the hyperinflammatory response. Prof. Stebbing's group was particularly interested in the effects of the JAK-STAT pathway on chemokines and cytokines.

At the time there was a global lockdown, and most labs were closed, but the team found some they could work with in Indiana, with Lilly, at Imperial College in Singapore, and at the Karolinska Institute in Sweden. They knew that baricitinib affected the JAK-STAT dependent cytokines, but they wanted to see whether it could affect the virus as well. They obtained frozen samples from rheumatoid arthritis trials showing that it reduced certain leukocyte subpopulations. And they demonstrated for the first time that higher doses of baricitinib led to reduced interleukin 6 levels in individuals without Covid but with arthritis. Using kinase assays, they also found out that it antagonised the host kinases. But what made baricitinib particularly intriguing was its unique capability to achieve this, surpassing both other JAK-STAT inhibitors and drugs that were believed to have off-target effects on these kinases. We know in the history of drug development that two molecules of the same class can have markedly different effects, for example, simvastatin and atorvastatin. Prof. Stebbing's group then performed organoid expression at Karolinska, and observed that administering cytokines to the organoids resulted in an elevation of ACE2 levels. Particularly remarkable was that baricitinib not only blocked the cytokine pathway, but also the drawbridge used by the virus, which was the ACE2 receptor. Between February and May 2020, the team published their findings in numerous papers. As predicted by AI, baricitinib inhibited the host kinases, dampened systemic inflammation, and also showed antiviral effects.

At this point, Prof. Stebbing published a paper in one of the Cell journals, calling for randomised trials. He even submitted a grant request to a UK grant body, which replied that a randomised control arm would have to be with hydroxychloroquine as the comparator. So, the team went ahead and used propensity score matching instead. They did a study with very elderly patients, with a median age of 81 years, who were in nursing homes. It was a once-daily tablet with dosing flexibility, 2 mg of 4 mg, no drug-to-drug interactions excreted, urine unchanged, and very few side effects, although there was some concern about clots. The researchers found that the cytokine response to

the virus was in a positive feedback loop. Using RNAc in liver organoids, baricitinib blocked that cytokine response and also downregulated the upregulated platelet genes responsible for the clotting caused by the virus. The researchers also performed super resolution microscopy with the Oxford Nanoimager, using nucleocapsid staining. They could see that baricitinib actually blocked the virus getting into the cells. They had some negative data like it would be expected, but a randomised control trial was really necessary. The trial, which enrolled 1,033 patients, started off as a placebo controlled RCT, but then remdesivir became licenced. So, the team had to adjust the randomised trial to baricitinib plus remdesivir versus remdesivir. Prof. Stebbing thought that baricitinib perhaps could help in the very early stage of the disease, but where it really worked was in patients with an ordinal scale of 4, 5, or 6 that were about to go to intensive care. On the other hand, monoclonal antibodies, like paxlovid and maybe molnupiravir, worked best before hospitalisation. Finally, based on the ACTT-2 study in November 2020, baricitinib got an FDA approval. Comparing the different RECOVERY trials, WHO SOLIDARITY, ACTT-1, ACTT-2 and COV-BARRIER, and looking only at the hazard ratio for mortality, by far the lowest ratio was in COV-BARRIER and ACCT-2.



Whilst the benefits of dexamethasone are seen in the sickest patients, JAK inhibitors such as baricitinib appear to work prior to ICU in ordinal scale 5, 6, with or without steroids. They likely work against all variants because they affect the host response. Mortality is a critical endpoint but what is also important is that they can be used in patients with a low GFR. Baricitinib has a very short half-life, unlike tocilizumab, which has a half-life of 13 days. When used for a short duration, JAK inhibitors are inexpensive, so suitable for low- or middle-income countries. The ACTT-4 trial in 2022 demonstrated that in hospitalised patients baricitinib plus remdesivir versus dexamethasone plus remdesivir was much better tolerated with fewer side effects, and it works as well, if not better.

A therapeutic from AI to FDA approval in 10 months is quite an achievement. But it would not have been possible without a global high-quality collaboration between pharmaceutical companies, smaller companies, the academia, colleagues, and smaller hospitals.