Episode 253 : Treatment and omicron

Dear colleagues,

Today's episode focuses on the questions how active the established specific anti-SARS-CoV-2 treatments are against omicron BA.1 and BA.2. In addition, I looked for evidence of resistance development against Remdesivir, Molnupiravir or Nirmatrelvir. And there is a final (??) negative judgment about Ivermectin.

First a table with all the (sometimes very confusing) names

Activity	Most used generic name	Trade name	Pro-drug or precursor	Active drug	Other names
Polymerase inhibitors	Remdesivir	Veklury	GS-5734	GS-443902 = triphosphate	
	Molnupiravir	Lagrevio	EIDD-2801	EIDD-1931 triphosphate	
3CL Protease inhibitor	Nirmatrelvir	Paxlovid*		PF-07321332	Bexovid
Neutralizing Anti-Spike monoclonal antibodies	Sotrovimab	Xevudy	S-309	VIR-7831	GSK4182136
	Imdevimab + Casirivimab	Ronapreve (EU) REGEN-COV (US)			REGN10987 + REGN10933
	Cilgavimab + Tixagevimab	Evusheld			COV2-2130 + COV2-2196
	Etesevimab + Bamlanivimab	(Eli Lilly co.)			LY-CoV016 + LY-CoV555

*Paxlovid is a combination of Nirmatrelvir and Ritonavir, added to slow down the liver catabolism

Ep 253-1: Rajal J Med Virol Genetic differences between variants

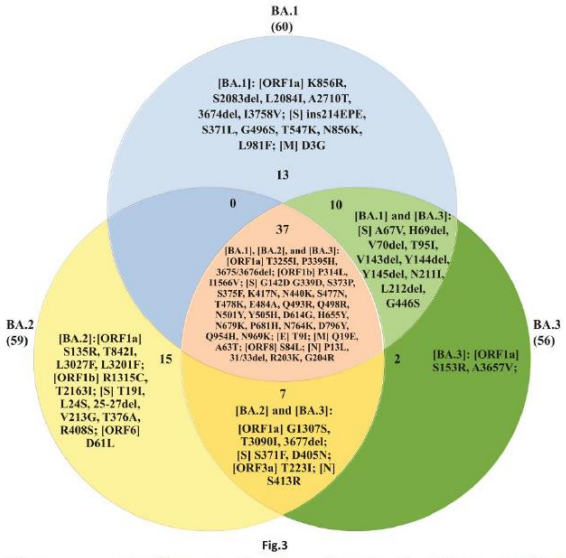


Figure 3. Venn diagram showing shared and unique mutations in the genomes of Omicron lineages BA.1, BA.2 and BA.3

As can be seen, Omicron has a number of mutations, not only in Spike, but also in ORF1 (encoding thevarious components of polymerase and protease). Moreover, some of these mutations are common to BA.1 and BA.2, while other are different. Hence, it is not immediately clear which anti-virals will remain active against which sub-variant.

Ep 253-2: Ohashi bioRxiv 28 Feb 2022 comparison of activity in several variants including omicron BA.1 and BA.2

Table 1. Estimated parameters for the antiviral effect of drugs

	IC_{50}	IC_{90}	m	IIP (C_{max})
casirivimab	(μg/ml)	(μg/ml)		
WK-521	0.0139	0.0713	1.3444	5.5662
QK002 (Alpha)	0.0136	0.0505	1.6747	6.9496
TY7-501 (Gamma)	0.0140	0.1666	0.8872	3.6706
TY11-927 (Delta)	0.0217	0.0749	1.7743	7.0029
TY38-873 (Omicron. BA.1)	> 10	-	-	-
TY40-385 (Omicron. BA.2)	> 10	-	-	-
imdevimab	(μg/ml)	(μg/ml)		
WK-521	0.0125	0.0963	1.0763	4.5202
QK002 (Alpha)	0.0227	0.0813	1.7221	6.7862
TY7-501 (Gamma)	0.0082	0.0416	1.3529	5.9296
TY11-927 (Delta)	0.0290	0.0834	2.0809	7.9787
TY38-873 (Omicron. BA.1)	> 10	-	-	-
TY40-385 (Omicron. BA.2)	1.2525	11.6931	0.9836	2.1658
S309	(μg/ml)	(μg/ml)		
WK-521	0.1587	0.7583	1.4048	4.0316
QK002 (Alpha)	0.0552	0.5449	0.9596	3.1943
TY7-501 (Gamma)	0.0384	0.1498	1.6143	5.6276
TY11-927 (Delta)	0.0870	0.2407	2.1589	6.7593
TY38-873 (Omicron. BA.1)	0.9579	2.6822	2.1348	4.4598
TY40-385 (Omicron. BA.2)	1.3579	62.2520	0.5744	1.1452
EIDD-1931	(μM)	(μM)		
WK-521	0.2270	0.7385	1.8626	2.9789
QK002 (Alpha)	0.3435	1.0099	2.0375	2.8922
TY7-501 (Gamma)	0.2432	0.6531	2.2241	3.4901
TY11-927 (Delta)	0.2828	1.4743	1.3307	2.0052
TY38-873 (Omicron. BA.1)	0.3407	1.6655	1.3846	1.9746
TY40-385 (Omicron. BA.2)	0.4614	1.0315	2.7310	3.5260
nirmatrelvir	(μM)	(μM)		
WK-521	1.8787	4.8869	2.5227	0.9858
QK002 (Alpha)	1.7795	6.5284	1.6904	0.7530
TY7-501 (Gamma)	1.6458	4.8727	2.0243	0.9244
TY11-927 (Delta)	1.7959	5.1161	2.0988	0.8828
TY38-873 (Omicron. BA.1)	1.8522	4.7245	2.3465	0.9403
TY40-385 (Omicron. BA.2)	1.9402	5.1784	2.2393	0.8653

Molnupiravir (EIDD-1931) and Nirmatrelvir keep good activity against both BA.1 and BA.2

Sotrovimab (S309) loses about 10 fold activity against both sublineages

Casivirimab and Imdevimab also pporly active against both sublineages

Ep 253-3: Takashita NEJM Feb 2022 focus on BA.2

Table 1. Efficacy of Monoclonal Antibodies and Antiviral Drugs against the Omicron/BA.2 Subvariant in Vitro.*

Monoclonal Antibody or Antiviral Drug	hCoV-19/Japan/UT-NCD1288-2N/2022 (Omicron/BA.2)	
	Tested Value	Factor Increase as Compared with the Ancestral Strain
Neutralization activity of monoclonal antibody†		
LY-CoV016, etesevimab	>50,000 ng/ml	>2749
LY-CoV555, bamlanivimab	>50,000 ng/ml	>10,661
REGN10987, imdevimab	68.65±8.84 ng/ml	22.5
REGN10933, casirivimab	1666.19±771.77 ng/ml	597.2
COV2-2196, tixagevimab	395.78±62.37 ng/ml	206.1
COV2-2130, cilgavimab	4.44±2.72 ng/ml	0.6
S309, sotrovimab precursor	1359.05±269.23 ng/ml	49.7
LY-CoV016 plus LY-CoV555	>10,000 ng/ml	>794
REGN10987 plus REGN10933	222.59±64.47 ng/ml	63.1
COV2-2196 plus COV2-2130	14.48±2.04 ng/ml	4.2
Viral susceptibility to drug‡		
GS-441524§	2.85±0.31 μM	2.7
EIDD-1931¶	0.67±0.22 μM	1.3
PF-07321332‖	6.76±0.69 μM	1.9

Etesevimab and Bamlanivimab essentially inactive against BA.2

REGN combination and Sotrovimab lose a lot (50- 60 X)

Evusheld still active, but based on Cilgavimab only

Remdesivir (GS-441524), Molunipiravir (EIDD-1931) and Nirmatrelvir (PF-07321332) fully active

Ep 253-4: Bruel medRxiv 12 March comparison BA.1 vs BA.2 v

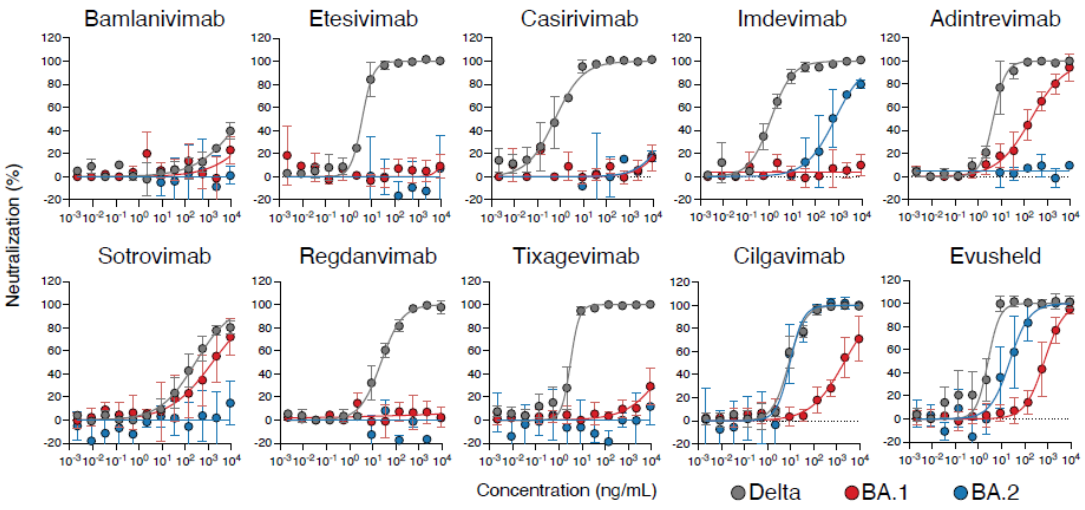


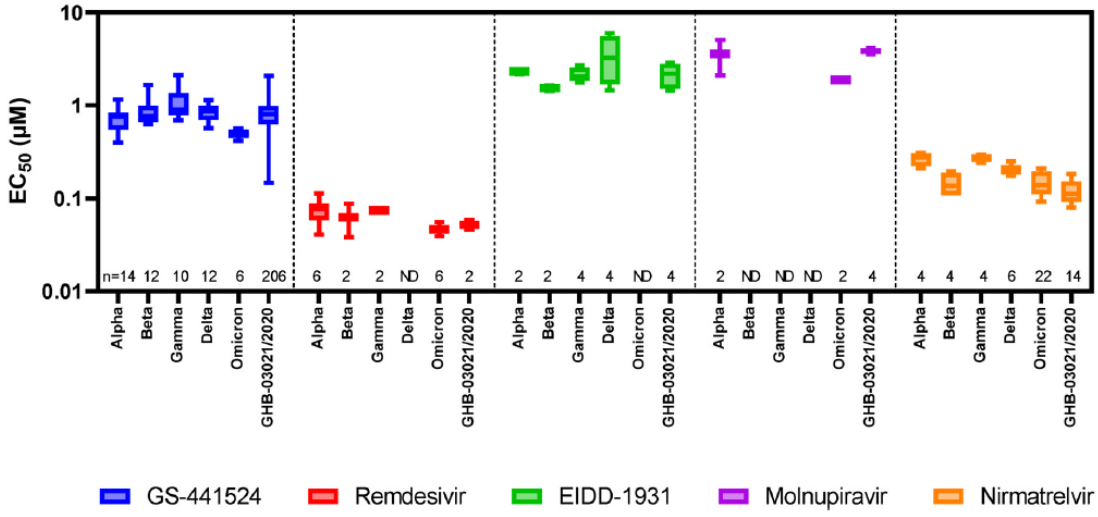
Figure 1 : Sensitivity of Omicron BA.2 to therapeutic monoclonals antibodies

Confirmation that

- The Eli Lilly cocktail (Bam-Ete) and the REGN cocktail (Casi-Imde) no longer useful for omicron
- Sotrovimab loses most activity against BA.2, but keeps activity against BA.1
- Evusheld keeps some activity against BA.2, less against BA.1 but fully dependent on Cilgavimab

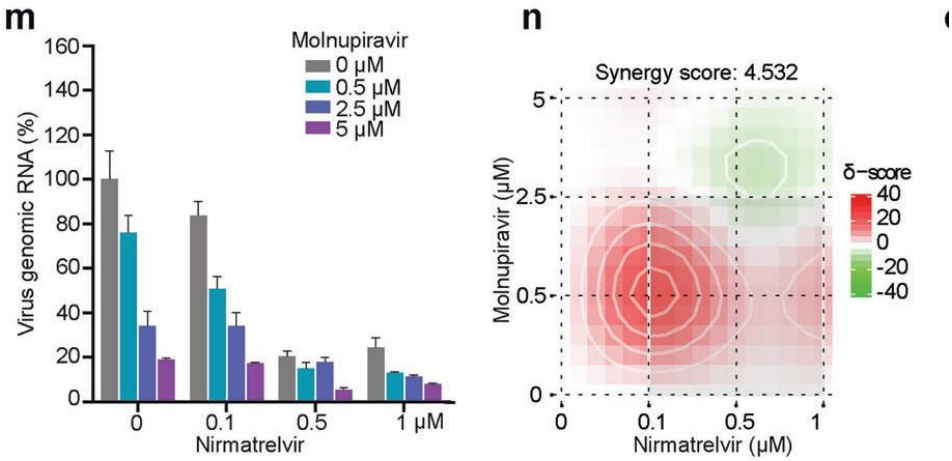
ALL THE FOLLOWING PAPERS FOCUS ON "OMICRON" , BUT IT IS IN FACT BA.1, since the work was carried out before BA.2 was prevalent.

Ep 253-5: Vangeel Antiv Res Feb 2022



Remdesivir, Molnupiravir and Nirmatrelvir are equally active against omicron (BA.1) as against other variants

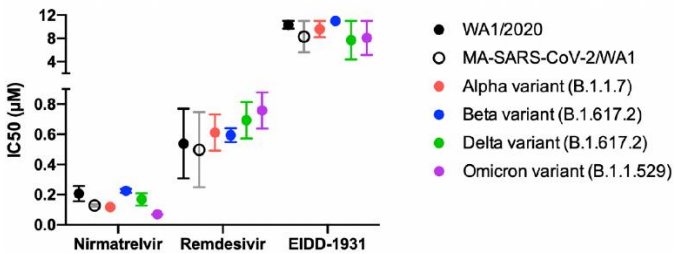
Ep 253-6: Pengfei Li Cell Res Jan 2022 : Omicron (BA.1) is sensitive to nirmatrelvir molnupiravir and the combination



The antiviral effects of combining molnupiravir and nirmatrelvir in WT SARS-CoV-2-infected Calu-3 cells based on intracellular viral RNA levels (n =3–4) shows **evidence of synergy**

Ep 253-7: Pitss bioRxiv Feb 2022 confirmation of activity Remdesivir against severel variants, including omicron BA.1

Ep 253-8: Rosales Jan 2022 Nirmatrelvir, Molnupiravir, and Remdesivir maintain potent *in vitro* activity against the SARS-CoV-2 Omicron variant (BA.1)



CONCLUSIONS :

1) **Remdesivir, Molnupiravir and Nirmatrelvir maintain full activity against omicron BA.1 and BA.2**
2) **The Regeneron and Eli Lilly mAb cocktails no longer useful against omicron BA.1 and BA.2**
3) **Sotrovimab loses all activity against BA.2 and has weak activity against BA.1: probably 10-fold higher doses needed**
4) **Evusheld: Tixagevimab compound inactive against both BA.1 and BA.2; Cilgavimab good activity against BA.2, but is very weak against BA.1.**

Obviously, in subjects with immunocompromise and chronic SARS-CoV-2 infection, the use of partly active mAb could result in induction of resistance-associated mutations.

Is there evidence of resistance development towards Remdesivir, Molnupiravir or Nirmatrelvir?

1) **Remdesivir: 2 papers found**

Ep 253-9: Szmiel PLoS Pathogens Sept 2021: in vitro selection of resistance towards Remdesivir.

After serial passage a single mutation **E802D** in the RNA-dependent RNA polymerase **NSP12**.

- Conferred only 2-2.5 fold resistance
- Associated with reduced fitness
- Associated with "spontaneous" mutations in Spike H69, E484, N501, H655, without immune pressure
- Is very rare in untreated subjects: 36 E802 mutations in > 800,000 sequenced cases (of which 24 E802D)

Ep 253-10: Shiv Gandhi Nat Comm March 2023: the same **E802D** mutation identified in **an immunocompromised patient** with acquired B-cell deficiency who developed an indolent, protracted course of SARS-CoV-2 infection in **2020** (ancestral COVID strain). This mutation was indeed associated with a moderate 6-fold resistance and reduced fitness of the virus.

The Remdesivir treatment was followed by Casivirimab + Imdevimab with reduction of viral load and improvement of clinical symptoms.

2) **Molnupiravir:** no evidence found in published studies. The mode of action of Molnupiravir is to induce hypermutations in SARS-CoV-2. Therefore, it is possible that Molnupiravir could facilitate development of resistance towards co-administered drugs.

3) **Nirmatrelvir:** no evidence found

The end of the Ivermectin saga?

As you remember, the worm-killer Ivermectin has been proposed as a cheap and effective COVID drug, based on in vitro activity against SARS-CoV-2 at very high concentrations and a presumed anti-inflammatory activity. Many small poorly controlled studies claimed a beneficial effect of Ivermectin, but there has always been a lot of scepticism.

Ep 253-11: Reis on behalf of TOGETHER consortium in NEJM 30 March

Double blind randomized controlled study in 3515 patients with at least one risk factor and within 7 days of diagnosis were treated with either Ivermectin 400 µg/kg or placebo once a day for 3 days

→ No difference in outcome = hospitalization due to COVID within 28 days.