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Two Antivirals and Monoclonal Antibodies for Immunocompromised Patients with New Variants of Sars-Cov-2. A Literature Review about the Next Frontiers of the Combination Therapy

Weimer LE[1,*], Cattari G[2], Fanales Belasio E[3], Cuccuru E[2] and Vidili Gianpaolo[2]

[1]*National Center for Global Health, Istituto Superiore di Sanità, Rome, Italy*
[2]*Day Hospital, Department of Medicine, Hospital Marino-Alghero, AOU Sassari, Sardegna, Italy*
[3]*Department of Infectious Diseases, DMI, Istituto Superiore di Sanità, Rome, Italy*

[*]**Corresponding author:** Liliana Elena Weimer, National Center for Global Health, Istituto Superiore di Sanità, Rome, Italy; E-mail: liliana.weimer@iss.it

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Abstract

The New Variants of COVID-19 continues to challenge global healthcare systems, particularly concerning vulnerable populations. Immunocompromised patients have a higher risk of severe outcomes when infected with SARS-CoV-2. This population is particularly vulnerable to prolonged viral replication, increased risk of breakthrough infections, and difficulties mounting an adequate immune response.

The emergence of variants of concern, particularly those with mutations in the spike protein, has complicated treatment strategies. After the first year period in which several treatments were employed early intervention strategies, including the use of antiretroviral and monoclonal anti bodies, have emerged as promising approaches to mitigate the severity of COVID-19 in fragile individuals and prevent disease progression, hospitalization and death even in recent time with less aggressive SARS-CoV-2 variants.

To date, information concerning the early treatments of COVID-19 using combined therapies has been limited. Literature data include individuals with different degrees of immunosuppression, a small sample size, different time when combination therapy was started, making it difficult to draw definitive conclusions. Moreover, some of them focused only on viral clearance effect, and not on major clinical outcomes.

In fact, as underlined in guidelines, high-quality data for combination treatment exploiting antivirals and neutralizing antibodies do not exist in the outpatient setting, especially in severe immunocompromised individuals.

Nevertheless, several studies have attempted to investigate the effect of this approach and although these are often observational studies without control groups, generally no severe adverse reactions from the combination therapy have been reported.

In this Literature Review we explain the Last Variant of Concern and the Updates on Combination Therapy for vulnerable persons with Sars-Cov-2.

Keywords: SARS-CoV-2; Monoclonal Antibodies

Introduction

SARS-CoV-2 variants of concern as of 20 December 2024

Variant classification serves as an important communication tool for alerting EU/EEA countries about the emergence of SARS-CoV-2 variants with concerning properties likely to impact the epidemiological situation in the EU/EEA. The ECDC Strategic Analysis of Variants in Europe (SAVE) Working Group is a

multidisciplinary team comprising of ECDC Experts working in Respiratory Viruses, Microbiology, Bioinformatics, Mathematical Modelling, Epidemic Intelligence, Emergency Preparedness and Response and Vaccine-Preventable Diseases and Immunisation. Currently meetings are held once per month to assess the observed or predicted impact of currently circulating and newly emerging SARS-CoV-2 variants in the EU/EEA and globally [1].

ECDC utilises three categories of variant classification to communicate increasing levels of concern about a new or emerging SARS-CoV-2 variant: variant under monitoring (VUM), variant of interest (VOI) and variant of concern (VOC). Classification criteria and recommended Member state actions are available here:

ECDC variant classification criteria and recommended Member State actions

New evidence is regularly assessed on variants detected through epidemic intelligence, genomic horizon scanning, or other scientific sources. If a decision is made to add, remove, or change the category for any variant, the tables are updated to reflect this change. The tables are regularly sent for consultation to ECDC stakeholders, such as the European Commission and WHO Regional Office for Europe's joint virus characterisation working group.

Variant surveillance data, including the distribution of VOC and VOI variant proportions in the EU/EEA and detailed country-specific COVID-19 epidemiological updates are available as part of the European Respiratory Virus Surveillance Summary (ERVISS).

Slides from the most recent SAVE WG meeting are available in EpiPulse, with SARS-CoV-2 variant classification updates also published in ECDC's Communicable Disease Threats Reports. To review a timeline of variant classification decisions, visit our change log. Following classification of a VOC or VOI, multiple closely related sub-lineages may emerge. To facilitate reporting of variant detections by countries to TESSy, a table listing sub-lineages assigned to VOCs and VOIs as of 5 December 2024 is available here. An additional table that includes sub-lineages assigned to VUMs as of 5 December 2024 is available here.

Description of the tables

The tables include:

Category: variant of concern (VOC), variant of interest (VOI), or variant under monitoring (VUM).

WHO label: As of 31st May 2021, WHO proposed labels for global SARS-CoV-2 variants of concern and variants of interest to be used alongside the scientific nomenclature in communications about variants to the public. This list includes variants on WHO's global list of VOC and VOI, and is updated as WHO's list changes.

Lineage and additional mutations: the variant designation specified by one or more Pango lineages and any additional characteristic spike protein changes. An alternate description may be used if the variant is not easy to describe using this nomenclature. For updated information on Pango lineages and definition of lineages and for instructions on how to suggest new lineages, visit the Pango lineages website. Each lineage in then table is linked to the respective lineage page on the Pango lineages website.

Country first detected: only present if there is moderate confidence in the evidence relating to the first country of detection.

Spike mutations of interest: not all spike protein amino acid changes are included – this is not a full reference for assignment of the variants. It includes changes to spike protein residues 319-541 (receptor binding domain) and 613-705 (the S1 part of the S1/S2 junction and a small stretch on the S2 side), and any additional unusual changes specific to the variant.

Year and month first detected: as reported in the GISAID EpiCoV database. This can be adjusted backwards in time if new retrospective detections are made.

Evidence concerning properties in three different categories:

- Transmissibility
- Immunity
- Infection severity

Each category is annotated as increased, reduced, similar, unclear, or no evidence depending on the currently available evidence. Increased or reduced means that there is evidence demonstrating that the property is different enough for the variant compared to previously circulating variants that it is likely to have an impact on the epidemiological situation in the EU/EEA. Similar means that there is evidence that demonstrates that the property is not different enough for this variant compared to previously circulating variants that it is unlikely to have an impact. Unclear means that the current evidence is preliminary or contradictory enough to make the assessment uncertain. No evidence means that no evidence has yet been evaluated for this category. The evidence is further annotated with v or m to indicate whether the evidence is available for the variant itself (v) or for mutations associated with the variant (m).

Transmission in the EU/EEA: categorized as dominant, community, outbreak(s), and sporadic/travel. The categories are qualitative, and the assessment is based on surveillance data collected in TESSy, GISAID EpiCoV data, epidemic intelligence data, and direct communications with the affected countries.

Variants of Concern (VOC)

As of 3 March 2023, ECDC has de-escalated BA.2, BA.4 and BA.5 from its list of SARS-CoV-2 variants of concern (VOC), as these parental lineages are no longer circulating. ECDC will continue to categories and report on specific SARS-CoV-2 sub-lineages in circulation that are relevant to the epidemiological situation. There are currently no SARS-CoV-2 variants meeting the VOC criteria.

Variants of Interest (VOI)

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Transmission in EU/EEA
Omicron	BA.2.86	n/a	I332V, D339H, R403K, V445H, G446S, N450D, L452W, N481K, 483del, E484K, F486P	n/a	Baseline (6)	Baseline (6-8)	Baseline	Community
Omicron	KP.3	n/a	Q493E, F456L	n/a	No evidence	No evidence	No evidence	Dominant
All sub-lineages of the listed lineages are also included in the variant. For the full list of lineages, please look at the table here.								

Variants under monitoring

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Transmission in EU/EEA
Omicron	XEC	n/a	T22N, F59S, F456L, Q493E, V1104L	n/a	No evidence	No evidence	No evidence	Community

These additional variants of SARS-CoV-2 have been de-escalated based on at least one the following criteria: (1) the variant is no longer circulating, (2) the variant has been circulating for a long time without any impact on the overall epidemiological situation, (3) scientific evidence demonstrates that the variant is not associated with any concerning properties.

De-escalated variants

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
Alpha	B.1.1.7	United Kingdom	N501Y, D614G, P681H	September 2020	Increased (v) (9)	Similar	Increased (v) (10, 11)	Drastically reduced

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								circulation in the EU/EEA following the emergence of Delta; little evidence of impact on vaccine induced immunity
n/a	B.1.1.7+E484K	United Kingdom	E484K, N501Y, D614G, P681H	December 2020	Increased (v) (9)	Increased (v) (12, 13)	Increased (v) (10)	Very low levels of circulation in the EU/EEA
Epsilon	B.1.427/B.1.429	USA	L452R, D614G	September 2020	Unclear (14)	Increased (v) (14)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA and available data indicating that vaccines and treatments are effective against such variant
n/a	B.1.616(c)	France	V483A, D614G, H655Y, G669S	February 2021	Detection (c) (15)	No evidence	No evidence	Not detected since 2021-04-23 (16)
Eta	B.1.525	Nigeria	E484K, D614G, Q677H	December 2020	No evidence	Increased (m) (12, 17)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
Theta	P.3	The	E484K,	January	Increased	Increased	No evidence	No longer

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
		Philippines	N501Y, D614G, P681H	2021	(m) (9)	(m) (12)		detected or detected at extremely low levels in the EU/EEA
Kappa	B.1.617.1	India	L452R, E484Q, D614G, P681R	December 2020	Increased (v) (18)	Increased (v) (19-22)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.620	Unclear (b)	S477N, E484K, D614G, P681H	February 2021	No evidence	Increased (m) (12, 23)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.617.3	India	L452R, E484Q, D614G, P681R	February 2021	Increased (m) ((9)1)	Increased (m) (12, 14)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.214.2	Unclear2	Q414K, N450K, ins214TDR, D614G	December 2020	No evidence	No evidence	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	A.23.1+E484K	United Kingdom	V367F, E484K, Q613H	December 2020	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	A.27	Unclear (b)	L452R, N501Y, A653V, H655Y	December 2020	Increased (m) (9)	Increased (m) (14)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	A.28	Unclear (b)	E484K, N501T, H655Y	December 2020	No evidence	Increased (m) (12)	No evidence	No longer detected or

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								detected at extremely low levels in the EU/EEA
n/a	C.16	Unclear (b)	L452R, D614G	October 2020	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.351+P384L	South Africa	P384L, K417N, E484K, N501Y, D614G, A701V	December 2020	Increased (v) (24)	Increased (v) (25, 26)	Unclear (27)	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.351+E516Q	Unclear (b)	K417N, E484K, N501Y, E516Q, D614G, A701V	January 2021	Increased (v) (24)	Increased (v) (25, 26)	Unclear (27)	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.1.7+L452R	United Kingdom	L452R, N501Y, D614G, P681H	January 2021	Increased (v) (9)	Increased (m) (14)	Increased (v) (10)	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.1.7+S494P	United Kingdom	S494P, N501Y, D614G, P681H	January 2021	Increased (v) (9)	Increased (m) (28)	Increased (v) (10)	No longer detected or detected at extremely low levels in the EU/EEA
Iota	B.1.526	USA	E484K, D614G, A701V	December 2020	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.526.1	USA	L452R, D614G	October 2020	No evidence	Increased (m) (14)	No evidence	Lineage withdrawn from Pango

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
n/a	B.1.526.2	USA	S477N, D614G	December 2020	No evidence	No evidence	No evidence	Lineage withdrawn from Pango
Zeta	P.2	Brazil	E484K, D614G	January 2021	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.1.519	Mexico	T478K, D614G	November 2020	No evidence	Increased (m) (14)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	AV.1	United Kingdom	N439K, E484K, D614G, P681H	March 2021	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	AT.1	Russian Federation	E484K, D614G, N679K, ins679GIAL	January 2021	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	C.36+L452R	Egypt	L452R, D614G, Q677H	December 2020	No evidence	Increased (m) (14)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	P.1+P681H	Italy	D614G, E484K, H655Y, K417T, N501Y, P681H	February 2021	No evidence	Unclear (29, 30)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
Mu	B.1.621	Colombia	R346K, E484K, N501Y, D614G, P681H	January 2021	Increased (m) (9)	Increased (m) (12)	No evidence	No longer detected or detected at extremely

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								low levels in the EU/EEA
Lambda	C.37	Peru	L452Q, F490S, D614G	December 2020	No evidence	Increased (v) (31, 32)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	AY.4.2	United Kingdom	L452R, T478K, D614G, P681R, A222V, Y145H	June 2021	Increased (v) (33)	Similar (v) (33, 34)	Similar (v) (33)	Delta sub-lineages will continue to be monitored within Delta VOC
n/a	B.1.1.318	Unclear (b)	E484K, D614G, P681H	January 2021	No evidence	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.617.2 + K417N	United Kingdom	L452R, T478K, D614G, P681R, K417N	June 2021	No evidence	No evidence	No evidence	Delta sub-lineages will continue to be monitored within Delta VOC
n/a	C.1.2	South Africa	D614G, E484K, H655Y, N501Y, N679K, Y449H	June 2021	Increased (m) (9)	Increased (m) (12)	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.617.2 + E484X (d)	India	L452R, T478K, D614G, P681R, E484X (d)	April 2021	No evidence	No evidence	No evidence	Delta sub-lineages will continue to be monitored within Delta VOC
n/a	B.1.617.2 + Q613H	India	L452R, T478K,	April 2021	No evidence	No evidence	No evidence	Delta sub-lineages will

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
			D614G, P681R, Q613H					continue to be monitored within Delta VOC
n/a	B.1.617.2 + Q677H	India	L452R, T478K, D614G, P681R, Q677H	April 2021	No evidence	No evidence	No evidence	Delta sub-lineages will continue to be monitored within Delta VOC
Beta	B.1.351	South Africa	K417N, E484K, N501Y, D614G, A701V	September 2020	Increased (v) (24)	Increased (v) (25, 26)	Increased (v) (11, 27)	No longer detected or detected at extremely low levels in the EU/EEA
Gamma	P.1	Brazil	K417T, E484K, N501Y, D614G, H655Y	December 2020	Increased (v) (35)	Increased (v) (36)	Increased (v) (11)	No longer detected or detected at extremely low levels in the EU/EEA
n/a	B.1.640	The Republic of Congo	D614G, F490R, N394S, N501Y, P681H, R346S, Y449N, 137−145de	September 2021	No evidence	No evidence	No evidence	No longer detected or detected at extremely low levels in the EU/EEA
n/a	XF	United Kingdom	Omicron-like	January 2022	No evidence	No evidence	No evidence	No longer detected.
n/a	XD	France	NTD Delta-like; remaining Omicron-like	January 2022	No evidence	No evidence	No evidence	No longer detected.
Delta	B.1.617.2	India	L452R, T478K, D614G, P681R	December 2020	Increased (v) (37)	Increased (v) (38-40)	Increased (v) (39, 41)	Detected at extremely low levels in the EU/EEA
Omicron	BA.1	South Africa and Botswana	(x)	November 2021	Increased (v) (42, 43)	Increased (v)(44-46)	Reduced (v) (47-49)	Detected at extremely low levels in

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								the EU/EEA
Omicron	BA.3	South Africa	(z)	November 2021	No evidence	No evidence	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	BA.2 + L452X	n/a	L452X	n/a	No evidence	Increased (50)	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	XAK	Germany		June 2022	No evidence	No evidence	No evidence	No longer detected.
Omicron	B.1.1.529 + R346X	n/a	R346X	n/a	No evidence	No evidence	No evidence	Instead of mutational proxies, tracking by lineages (majorly BQ.1 and BF.7)
Omicron	B.1.1.529 + K444X, N460X	n/a	K444X, N460X	n/a	No evidence	Increased (m)(51)	No evidence	Instead of mutational proxies, tracking by lineages (majorly BQ.1)
Omicron	B.1.1.529 + N460X, F490X	n/a	N460X, F490X	n/a	No evidence	Increased (m)(51)	No evidence	Instead of mutational proxies, tracking by lineages (majorly BA.2.75 and XBB)
Omicron	BA.2.3.20	n/a	K444R, L452M, N460K	n/a	No evidence	No evidence	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	BF.7	n/a	R346T, F486V	n/a	No evidence	No evidence	No evidence	Detected at extremely low levels in

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								the EU/EEA
Omicron	BA.2	South Africa	(y)	November 2021	Increased (v)(42, 52)	Increased (v) (46)	Reduced (v)(53, 54)	Parental lineages are no longer circulating, ECDC monitoring sub-lineages in circulation
Omicron	BA.4	South Africa	L452R, F486V, R493Q	January 2022	No evidence	Increased(50, 55)	No evidence	Parental lineages are no longer circulating, ECDC monitoring sub-lineages in circulation
Omicron	BA.5	South Africa	L452R, F486V, R493Q	February 2022	No evidence	Increased(50, 55)	Unclear (56)	Parental lineages are no longer circulating, ECDC monitoring sub-lineages in circulation
Omicron	XBC (x)	n/a	N440K, F486P	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	BN.1	n/a	R346T, K356T, F490S,	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	XAY	n/a	F486P	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	BQ.1	n/a	K444T, N460K	n/a	Increased (5)	Increased (2, 3, 61-63)	Unclear (64)	Detected at extremely low levels in the EU/EEA
Omicron	XBB (z)	n/a	N460K, F490S	n/a	Increased (1)	Increased(57-61)	Unclear(62)	Detected at extremely low levels in

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
								the EU/EEA
Omicron	CH.1.1	n/a	K444T, L452R	n/a	Increased (1, 63)	Increased (v) (57, 58, 60, 64)	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	XBB.1.16	n/a	E180V, T478R, F486P	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	BA.2.75	India	W152R, F157L, I210V, G257S, D339H, G446S, N460K, Q493 (reversion)	May 2022	Unclear (65)	Similar to Baseline (5 7, 58, 66)	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	DV.7.1	n/a	K444T, L452R, L455F	n/a	No evidence	No evidence	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	XBB.1.5-like + L455F + F456L	n/a	**L455F**, **F456L**, N460K, S486P, F490S	n/a	No evidence	No evidence	No evidence	Detected at extremely low levels in the EU/EEA
Omicron	BA.2.87.1	South Africa	(q) (e)	2023 September	No evidence	No evidence	No evidence	Not detected in EU/EEA
Omicron	XBB.1.5-like	United States	N460K, S486P, F490S	n/a	Similar to Baseline (1, 2)	Reduced (v) (1, 3, 5)	Similar to Baseline (4)	No longer detected or detected at extremely low levels in the EU/EEA
Omicron	BA.2.86 + R346T + F456L	n/a	R346T, F456L		No evidence	No evidence	No evidence	Decreased to low proportions in EU/EEA
Omicron	BA.2.86 + R346T	n/a	R346T		No evidence	No evidence	No evidence	Decreased to low proportions in EU/EEA

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Rationale for de-escalation
Omicron	BA.2.86 + F456L	n/a	F456L		No evidence	No evidence	No evidence	Mutation present in the majority of circulating descendants

x: A67V, Δ69-70, T95I, G142D, Δ143-145, N211I, Δ212, ins215EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F
y: G142D, N211I, Δ212, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K
z: A67V, Δ69-70, Δ143-145, N211I, Δ212, G339D, S371F, S373P, S375F, D405N, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, D796Y, Q954H, N969K
q: G75D,S98F,V126A,W152L,R190S,K417T,K444N,V445G,L452M,N481K,V642G,K679R,S691P,T791I,Y796H,D936G
n/a: not applicable, no WHO label has been assigned to this variant at this time
All sub-lineages of the listed lineages are also included in the variant, e.g., B.1.429.1 is included in B.1.427/B.1.429 as it is a sub-lineage of B.1.429.
(a) No assessment of transmission is given for variants in the monitoring category, only detected/not detected.
(b) The earliest detections from several different countries are close in time and there is no clearly demonstrated travel link to a specific country that explains the detections.
(c) The property of concern for this variant was the fact that there are reports of difficulties associated with detecting it in upper respiratory tract samples. These difficulties were not caused by primer-template mismatch but rather by the virus not being present in sufficient quantities in the upper respiratory tract.
(d) Any amino acid substitution
(e) Preliminary mutations based on a limited number of genomes

Combination therapy for Immunocompromised Patients

Combination treatment with two Antivirals and Monoclonal Antibodies for Immunocompromised Patients with New Variants of Sars-Cov-2 seems an effective and well tolerated (<5% reported bradycardia, hepatotoxicity, neutropenia) strategy for treating prolonged/relapsed SARS-CoV-2 infections in the immunocompromised host, although its optimal composition and duration cannot be defined based on the currently available evidence [2].

The role of combination treatment as an early treatment strategy for vulnerable patients at a high risk of progression to severe disease/persistent shedding requires further evidence from comparison with immunotherapy, even though high efficacy was reported for combinations of antivirals plus mAbs in case of previous viral variants.

Update on Clinical Trials about Early Combination therapy for vulnerable Patient with New Variants

Early administration of combination therapy with one direct antiviral agent and the monoclonal antibody sotrovimab in immunocompromising patients is associated with high viral clearance, low risk of progression, hospitalization and death.

Persisting viral replication in immunocompromised hosts increases the risk of selecting SARS-Cov-2 variants, which escape from antibody neutralization mutations which increase antiviral resistance, especially when patients are exposed to multiple therapies in the attempt of reaching virological clearance. In the light of this, despite a clear evidence supporting this approach, the combination therapy with one anti-viral and a mAb, or two antiviral, with or without a mAb, has become increasingly recommended by experts to treat persistently infected patients, although based on personal opinion or small non-controlled studies [3]. To date, only a few authors have studied the systematic use of combination therapies in immunocompromised subjects, and these studies mostly reported the use of combination therapy in patients who had already developed prolonged or persistent COVID-19 mostly hospitalized. For example, Mikulska et al. reported the use of combination therapy only in hospitalized patients after a median time of 42 (IQR 29–100) days from SARS-C infection, with response rates of 75%, 73%, and 82% at day 14, day 30, and last follow-up, respectively [4]. Similarly, D'Abramo et al. recently

reported the use of combination therapy in a cohort of 69 immunosuppressed patients hospitalized for severe COVID-19 (92 required oxygen therapy) and treated a median of 21 (IQR 8–36) days from symptom onset [5]. Interestingly in this study, the use of monoclonal antibodies (tixagevimab/cilgavimab or sotrovimab) in the antiviral combination was associated with a significantly higher rate of viral clearance [5]. In both of the abovementioned studies, the duration of viral shedding was longer than that in our study, but treatment was started later during the course of infection. On the other hand, a recently published paper by our group analyzed the efficacy and safety of the combination of two antivirals, with or without a mAb, both in early (within 10days from symptoms) and in the later phase (after 10days) of SARS-CoV-2 infection immunocompromised subjects, finding that 100% of the patients treated early reached virological clearance at day 30 from the end of the therapy and were alive and well at follow-up, whereas the corresponding figures in the late-treated patients were 50% and 75%, with patients in the late group more frequently needing oxygen supplementation (p=0.015), steroid therapy (p=0.045), and reaching higher COVID-19 severity (p=0.017) [6].

In line with this, Orth and colleagues have recently presented the largest cohort (144 subjects, of which 82% were immunocompromised) of patients treated with combination therapy [5], according to co-primary endpoints (prolonged viral shedding at day 21 after treatment initiation and days with SARS-CoV-2 vi load ≥ 106 copies/ml).

The authors found that underlying hematological malignancies and treatment initiation later than five days after diagnosis were significantly associated with longer viral shedding, which [7] was confirmed and consolidated by our results, since we found a significantly higher proportion of patients with prolonged infection (64%) among those who started antiviral therapy later than 3days after symptoms comparing our results to historical cohorts, we found a great reduction in mortality and needing for mechanical ventilation, when we consider observational studies with low prevalence of early antiviral or mAb use [8], but also a low prevalence of hospital admission (4%) and persistent infection (1.6%) in immunocompromised patients who receive early treatment with N/r alone [9].

Recently, Mazzitelli et al. have published a retrospective study comparing 30-day mortality, access to emergency department and hospitalization between immuncompromised COVID-19 patient treated with antivirals alone and antivirals plus sotrovimab [10]. They found that no significant differences were observed between the two groups for the outcomes taken individually, but, after applying a propensity score weighted approach, they found that combination therapy, and both altered liver and kidney function, were significantly associated with the composite outcome, in a favorable and unfavorable manner, respectively [10]. These contrasting findings need to be further analyzed with new studies specifically aimed to comparing monotherapy versus combination therapy in immunocompromised patients.

Monoclonal Antibodies for Immunocompromised Patients

As of January 2025, monoclonal antibodies (mAbs) continue to play a crucial role in managing COVID-19 among immunocompromised patients, who are at increased risk for severe and prolonged illness. These therapies are employed both for pre-exposure prophylaxis and for treatment upon infection.

Pre-Exposure Prophylaxis

Pemivibart (Pemgarda™) is currently the only long-acting monoclonal antibody authorized in the United States for pre-exposure prophylaxis in individuals who are moderately or severely immunocompromised and unlikely to mount an adequate immune response to COVID-19 vaccination. Administered via intravenous infusion, Pemivibart provides an additional layer of protection for those at high risk.

In Europe, Sipavibart (marketed as Kavigale) has been recommended for marketing authorization by the European Medicines Agency (EMA) for the prevention of COVID-19 in immunocompromised individuals aged 12 and older. This recommendation, adopted in December 2024, reflects ongoing efforts to expand prophylactic options for vulnerable populations.

Treatment of active infection

The effectiveness of monoclonal antibody treatments can be influenced by the emergence of new SARS-CoV-2 variants, which may evade certain therapies. Consequently, the therapeutic landscape is continually evolving, with new monoclonal antibody combinations being investigated to counteract immune evasion and improve outcomes for immunocompromised patients.

Early mAb Therapies (Pre-Omicron)

- Bamlanivimab + Etesevimab (Eli Lilly) and Casirivimab + Imdevimab (Regeneron) were early mAb combinations approved for emergency use in COVID-19 treatment.
- These mAbs were highly effective against earlier strains like Alpha and Beta, but their efficacy decreased against variants like Delta and Omicron, due to mutations in the spike protein, which reduced the ability of these mAbs to bind effectively.

Omicron and Beyond

Newer mAbs, such as Tixagevimab + Cilgavimab (Evusheld), have shown broader neutralization activity against Omicron and its subvariants. These combinations have become the gold standard for pre-exposure and post-exposure prophylaxis in immunocompromised patients.

However, Bebtelovimab (Eli Lilly) was an mAb that showed effectiveness against multiple subvariants of Omicron. Despite this, its effectiveness waned with further viral mutations. Other emerging mAb therapies are being designed to target a broader range of variants.

Antiviral Agents for Immunocompromised Patients

Antiviral agents have proven crucial in preventing the replication of SARS-CoV-2 and reducing the viral load in infected individuals. Immunocompromised patients, who often struggle to mount an immune response, benefit significantly from antiviral therapies [11].

Remdesivir

1. Remdesivir, a nucleoside analog, was one of the first antivirals authorized for emergency use during the pandemic. It has been shown to reduce hospitalization time and improve outcomes in hospitalized patients.
2. Effectiveness against variants: Remdesivir remains effective against a wide range of variants, making it a staple in COVID-19 treatment. However, it must be administered early in the disease course to maximize its benefit.

Paxlovid (Nirmatrelvir + Ritonavir)

Paxlovid has emerged as one of the most effective antiviral therapies, especially when administered early in the course of infection. It works by inhibiting the SARS-CoV-2 protease, essential for viral replication.

Challenges with Immunocompromised Populations: The combination of nirmatrelvir and ritonavir can interact with certain immunosuppressive drugs, requiring careful monitoring and dose adjustment in patients receiving immunosuppressive therapies.

Resistance and Variants: Studies have shown that Paxlovid remains effective against most SARS-CoV-2 variants, but the emergence of certain mutations (e.g., in the protease) may pose a challenge for long-term efficacy.

Molnupiravir

Molnupiravir is another antiviral option that targets the viral RNA polymerase, leading to errors in the virus's RNA. While it is generally less effective than Paxlovid, it remains a viable option for patients who cannot take Paxlovid due to drug interactions.

Broad Spectrum: Molnupiravir has shown some potential to work against various variants, though resistance to the drug could emerge with prolonged use [12].

Triple Combination Therapy: The New Frontier

As the COVID-19 pandemic evolves, researchers are exploring the potential of combining two antivirals with monoclonal antibodies for immunocompromised patients. The rationale for this combination is that it targets multiple points in the viral life cycle, thereby minimizing the likelihood of resistance and improving treatment outcomes.

Recent studies Gentile et al. [3] suggests that early administration of combination therapy with sotrovimab and a direct antiviral agent is safe and could be effective in preventing hospitalization, progression to severe COVID-19, and the development of prolonged/persisting SARS-CoV-2 infection in severely immunocompromised patients.

The circulation of new variants could prevent the efficacy of this strategy due to the loss of efficacy of sotrovimab.

Rationale for Triple Therapy

Monoclonal Antibodies: These therapies provide immediate neutralizing effects by binding to the spike protein of the virus, preventing it from entering host cells [13].

Antivirals (Remdesivir + Paxlovid): Remdesivir inhibits viral replication early in infection, while Paxlovid prevents the protease from processing viral proteins necessary for replication.

Synergistic Effects: The combination of mAbs with two antiviral agents could provide broad protection against a wider range of variants, especially those with mutations that escape one particular treatment [14].

Clinical Evidence and Ongoing Trials

Several clinical trials are investigating the safety and efficacy of triple combination therapy. Preliminary results indicate that a combination of Paxlovid + Remdesivir + Evusheld may offer synergistic antiviral and immune-enhancing benefits, especially in immunocompromised patients.

Early Findings: Triple therapies may significantly reduce viral loads, accelerate viral clearance, and lower the incidence of severe disease in high-risk populations.

Challenges and Considerations: Triple combination therapy presents several challenges, including potential drug-drug interactions, cost, and accessibility, particularly for resource-limited settings. Close monitoring for adverse effects and drug interactions, particularly in immunocompromised individuals, is crucial.

Preclinical and Clinical Evidence for Triple Therapy

- Review studies that have tested combinations of two antivirals (e.g., Remdesivir + Molnupiravir) and monoclonal antibodies (e.g., Casirivimab/Imdevimab).
- Research from major clinical trials, such as ACTIV-3 and RECOVERY, showing positive results from combination therapies.
- Data showing improved viral clearance, reduced hospitalization, and decreased mortality in immunocompromised patients.

Challenges and Considerations

- **Safety**: Risks of drug interactions, toxicity, and long-term effects of triple therapies need to be evaluated.
- **Cost**: The financial burden of triple therapies may limit access, especially in low-resource settings.
- **Variants**: Ongoing mutations of the SARS-CoV-2 virus, potentially diminishing the effectiveness of current treatments.

Conclusion

The emergence of new variants of SARS-CoV-2 has underscored the need for more robust and adaptive therapeutic strategies. Triple combination therapy involving two antivirals and monoclonal antibodies appears to offer an exciting new approach for treating immunocompromised patients. As the virus continues to evolve, the development of broad-spectrum therapies, along

with personalized approaches to treatment, will be crucial in managing COVID-19 in immunocompromised individuals.

The integration of dual antiviral therapies with monoclonal antibodies could be the best therapeutic strategy, offering a more comprehensive and durable response against evolving SARS-CoV-2 variants.

Recent studies suggests that early administration of combination therapy with sotrovimab and a direct antiviral agent is safe and could be effective in preventing hospitalization, progression to severe COVID-19, and the development of prolonged/persisting SARS-CoV-2 infection in severely immunocompromised patients.

The circulation of new variants could prevent the efficacy of this strategy due to the loss of efficacy of sotrovimab.

Further studies are needed to compare the combination approach with monotherapy in these categories, especially considering the reduced activity of the monoclonal compound.

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