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REVIEW

The Emergence of Escape Mutations in COVID-19 Following Anti-Spike Monoclonal Antibody Treatment: How Do We Tackle It?

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Abstract: Treatment-emergent resistance to anti-Spike monoclonal antibody (mAb) was a largely unexpected and dramatic finding along the COVID-19 pandemic. Emergence of resistant strains was particularly common in immunocompromised patients, who often harbored very high SARS-CoV-2 loads when treated with mAb monotherapies. Concerns were raised regarding the risk for some of those resistant variants to propagate in communities. In this review, we will summarize the experience thus far and suggest recommendations to prevent and manage mAb treatment-emergent resistance such as comboing and reliance over polyclonal immunoglobulins.

Keywords: monoclonal antibodies, spike, treatment-emergent resistance

Introduction

Before the end of the first year of the COVID-19 pandemic, marketing authorizations of anti-Spike monoclonal antibodies (mAb) represented a milestone achievement for drug development.[1,2] These immunoglobulins were developed very rapidly going from pre-clinical laboratory research to clinical trials in a matter of months. Initially evaluated for the treatment of COVID-19 inpatients with poor results,[3] anti-Spike mAb's were soon retargeted to outpatients for preventing COVID-19 progression and hospitalizations, where they proved to be successful as long as they bound to SARS-CoV-2.[4] When mass vaccination campaigns combined with ongoing infection waves achieved immunity in the majority of the population, anti-Spike mAb's were again retargeted to the treatment of inpatients with severe COVID-19 to reduce mortality, with mixed results and subgroup analysis showing clear benefit only in immunocompromised (IC) patients, who were emerging as a vulnerable population at high risk for severe COVID-19.[5] Importantly, no randomized controlled trial (RCT) of small molecule antiviral or anti-Spike mAb were ever specifically conducted in an IC population, except for COVID-19 convalescent plasma (CCP),[6,7] with supporting evidences for small-molecule antivirals exclusively stemming from small subgroup analyses of larger RCTs targeting the general population. In the IC setting, unpredicted consequences of anti-Spike mAb use occurred, of which the most concerning one was the onset of treatment-emergent resistance. Treatment-emergent resistance in IC patients is likely facilitated by the very high viral loads found in such individuals at the time of treatment initiation that, even when fully sensitive at baseline, are subject to selective immune pressures exerted by both the host immune system and the therapeutic mAb. The higher the viral load, the more likely there are mAb-resistant variants and the easier it is a for a mAb-resistant viral clone to emerge and multiplicate. IC patients have a 5.6-fold increased risk of developing Spike mutations (regardless of sex, age, level of IgG anti-S, variant, and mAb treatment) compared to non-IC patients, which are associated with a prolonged duration of viral clearance but no clinical worsening,[8] which likely reflect the inability to mount the exaggerated inflammatory response associated with COVID-19 progression. Nevertheless, persistent infection could translate into direct clinical damage if a novel or more potent immunosuppressive treatment is initiated, and consequently IC patients often experience delay in the required treatments, which represents a major problem for hem-onc patients.

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At that point clinical virologists have to face 2 problems: the first is clearly to retreat the patient with more effective antivirals, and the second is to monitor the spread of the mutated variant in the community. In this review, we will focus on the prevention and management of anti-Spike mAb treatment-emergent resistance in SARS-CoV-2.

Epidemiology

Table 1 summarizes all cases of treatment-emergent anti-Spike mAb resistance reported in the medical literature. On June 20 2025, we searched PubMed and medRxiv repositories for literature published since January 1 2020using English language as a restriction. We used the query "('sotrovimab' OR 'tixagevimab' OR 'cilgavimab' OR 'bamlanivimab' OR 'etesevimab' OR 'casirivimab' OR 'imdevimab' OR 'bebtelovimab' OR 'regdanvimab' OR 'sipavibart' OR 'pemivibart') AND. ('resistance' OR 'escape' OR 'evasion' OR 'evolution')". We excluded studies reporting in vitro data only, all clinical studies not reporting viral genome sequencing data, all primary research on baseline (as opposed to treatment-emergent) resistance, and all

Table 1 Published Cases of Anti-Spike mAb Treatment-Emergent Resistance as of June 20, 2025

Anti-Spike mAb(s)	N (of n) Cases	SARS-CoV-2 Strain	Spike Mutations	Ref
Bamlanivimab monotherapy (700 mg iv)	7 out of 101 (6.9%) immunocompetent patients	n.a.	E484K/Q, S494P	Choudhary et al[9–11]
	1 immunocompromised patient	Alpha	E484K, Q493R	Truffot et al[12]
	1 immunocompromised patient	Alpha	E484K, Q493R, S494P	Lohr et al[13]
	5 out of 6 (83.3%) immunocompromised patients	B.1	E484K →E484Q, reverted to E484K after CCP	Jensen et al[14]
	1 immunocompromised patient	Alpha	E484Q	Bronstein et al[15]
	2 immunocompromised patients	20B/20G	E484Q/K	Simons et al[16]
	1 immunocompetent patient	B.1.311	E484K	Sabin et al[17]
	1 immunocompromised patient	B.1.2	E484T	Halfmann et al[18]
	2 immunocompromised patients	20A.EU2 / 20I/501Y.V1	E484A/K	Destras et al[19]
	1 immunocompromised patients	B.1.177.81	E484K S494P	Schoefbaenker et al[20]
	2 immunocompromised patients	Alpha?	E484Q/K, Q493R	Scherer et al[21]
	5 out of 45 (11.1%)	Alpha	E484A/K, Q493R, S494P	Gupta et al[22]
	3 immunocompromised patients	20A.EU.2	E484K	Boussen et al[23]
	1 out of 2 (50%) immunocompetent	B.1.214.2 Alpha	Q493R	Jary et al[24]
	5 out of 6 (83.3%)	Alpha	E484A/K, Q493R, S494P	Peiffer-Smadja et al[25]
Bamlanivimab 700 mg + etesevimab 1400 mg cocktail	1 out of 102 (1%) patients	B.*	S494P	Gottlieb et al[26]
	1 immunocompromised patient	Alpha	Q493R	Focosi et al[27]
	1 immunocompromised patient		Q493R	Guigon et al[28]
	5 out of 23 (21.7%) patients (17 immunocompromised)		E484K, Q493R	Vellas et al[29]
	3 out of 108 (2.8%)		E484D, Q493R/K	Gupta et al[22]
	1 out of 3 (33%)		Q493R	Jary et al[24]
	12 out of 28 (42.9%)		E484K, Q493K/R	Zafilaza et al[30]
	5 out of 34 (14.7) patients (5 with B-cell malignancies)		Q493R, E484D	Pommeret et al[31]

(*Continued*)

Table 1 (Continued).

Anti-Spike mAb(s)	N (of n) Cases	SARS-CoV-2 Strain	Spike Mutations	Ref
Casirivimab + imdevimab (REGN-CoV) cocktail	1 immunocompromised patient	n.a.	E484K/A, Y489H, Q493K and N501Y	Choi et al[32]
				Clarke et al[33]
	1 out of 14 (7%)	Delta	G446V, E484Q	Huygens et al[34]
	1 immunocompromised patient	AY.29	L452R	Iwasaki et al[35]
	2 out of 74 (2.7%) immunocompromised patients	Delta	G446V, G446V+Y453F	Leducq et al[36]
	1 out of 17 (5.9%)	Alpha	E406G	Gupta et al[22]
	15 out of 160 (9.4%)	Delta, BA.1	E406D/Q, G446S/V, Y453F, L455F/S	Ragonnet-Cronin et al[37]
Sotrovimab	4 cases out of 100 (4%)	Delta	E340K/A/V	Rockett et al[38]
	10 cases out of 18 (55.6%) (15 immunocompromised)	BA.1 (94%)	E340K/A/V/D/G/Q, P337L/R/S	Birnie et al[39]
		BA.2 (6%)		
	3 out of 16 (18.8%) immunocompromised patients	2 BA.1, 1 BA.2	E340D	Focosi et al[40]
	18 out of 34 (52.9%) immunocompromised patients	17 BA.1	P337L/S, E340A/K/D/G, K356T, S371F	Vellas et al[41]
		1 BA.2		
	4 of 25 (16%) BA.1-infected patients 2 of 7 (28.6%) BA.2-infected	BA.1	P337X, E340X	Huygens et al[42]
		BA.2		
	5 out of 21 (24%)	BA.1/2	P337D/L/S, E340Q/Y/V, V483A, S490F, D796Y	Huygens et al[34]
	5 out of 8 (62.5%) immunocompromised	BA.1 (7)	P337L/R, E340D/R/K/V/Q, R346T, K356T	Andrés et al[43]
		AY.100 (1)		
	40 out of 170 (23.5%)	BA.1/2 ?	L335S, P337L/R, E340A/K/V, N343S/Y, A344V, R346G, K356R, S359G, N360D, C361T, R509I	Subramanian et al[44]
	8 patients	BA.1	P337R/S, E340A/D/K/Q	Destras et al[45]
	9 out of 34 (26.5%)	BA.1.1.* (n=14)	E340K/D/V	Gupta et al[22]
		BA.1 (n = 13)		
		BA.2 (n = 7)		
	54 out of 134 (40.3%) patients	Delta, BA.1, BA.2	P337R/S, E340A/D/K/V, K356T	Ragonnet-Cronin et al[37]
	15 out of 22 (68%) patients	BA.5	P337S/R/T/L/A/H, E340A/D/K/Q/V/G, R346T and K356T	Palomino-Cabrera et al[46]
	68 out of 166 (41%) immunocompromised patients	Delta	P337S/R/L/H, E340D/K/A/Q/V/G, K356T/R	Leducq et al[36]
	47 out of 156 (30.1%) patients	BA.4/5	P337L/S, E340A/D/G/K/Q/V, and K356R/T	Breuer et al[47]
	1 immunocompromised patient	Alpha?	E340A/D, F342insLTRMV	Iriyama et al[48]
	1 immunocompromised patient	BA.1	E340D	Marques et al[49]
	1 immunocompromised patient	Delta	E340A/K/V	Tanino et al[50]

(*Continued*)

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Table 1 (Continued).

Anti-Spike mAb(s)	N (of n) Cases	SARS-CoV-2 Strain	Spike Mutations	Ref
	1 immunocompromised patient	XBB?	E340Q	Bolis et al[51]
	1 immunocompromised patient	BA.1.1.16	E340A	Mazzetti et al[52]
	14 out of 43 (32.6%) patients	BA.1	P337S/H/L/R, E3[51] 40K/D/V	Gliga et al[53]
Cilgavimab-tixagevimab	9 out of 18 (50%) immunocompromised cases	BA.2	K444R/N, R346T, L452M	Vellas et al[54]
	20 out of 235 (8.8%) immunocompetent patients (2.1% at allele frequency > 25%)	Alpha (39.7%), BA.1 (17.6%), Gamma (11.3%), Delta (9.7%)	C488Y, E484V, L452R, S477R, T478K	Kijak et al[55]
	16 out of 24 (68%) immunocompromised patients	Delta	R346K/I/T/S, K444R/N/M	Leducq et al[36]
	3 out of 14 (21%)	BA.2 (2), BA.5 (1)	K444R/N, S371F	Huygens et al[34]
	1 out of 22 (4.5%) immunocompetent patients	BA.4/5	K444N	Gruber et al[56]
Bebtelovimab	1 immunocompromised patient	BA.1.23	V445A	Gonzalez-Reiche et al[57]
	5 out of 6 (83%) immunocompromised patients	Alpha/Delta		Sanchez et al[58]
	1 immunocompromised patient	XBB.1	K444N	Marques et al[49]

Notes: * = PANGO lineage descendants; ? = SARS-CoV-2 lineage not determined by genome sequencing and inferred from historical epidemiological data.

secondary research. We collected data about sample size, underlying immunosuppression and incidence of de novo mutations at Spike residues associated with anti-Spike mAb escape.

Clearly, anti-Spike mAb monotherapies, such as bamlanivimab or sotrovimab, were associated with exceedingly high resistance rates peaking at 60% in real-world evidences among IC patients. Phan et al demonstrated that bamlanivimab, in the models with best-fit parameters, selects for resistance mutants that can expand to high levels due to target cell replenishment, with the ultimate clearance of virus however being dependent on the development of adaptive immunity.[59] How treatment-emergent resistance relates to clinical progression has been investigated in placebo-controlled RCTs for sotrovimab (COMET-ICE: 23.5 vs 3.8% at allele frequencies > 5%)[44] and tixagevimab/cilgavimab (TACKLE: 8.5 vs 5.3%, 2.1% vs.0% considering allele frequencies > 25%).[55] Although the allele frequency thresholds are low and could be judged irrelevant, the follow-up in those RCTs was very short, and allele frequencies would have likely been much higher at later timepoints.

In the case of sotrovimab, it is noteworthy that incidence was much lower in company-sponsored studies, likely highlighting a possible recruitment bias towards patients with highly functioning immune systems relative to real-world participants.[44]

Preventing Treatment-Emergent mAb Resistance

Appropriateness

Appropriateness, ie, the delivery of an mAb against a SARS-CoV-2, which retains baseline sensitivity, represents the first pillar of prevention. Infection by a SARS-CoV-2 lineage in IC patients invariably leads to a swarm of viral quasi-species.[60] In patients infected by basally resistant SARS-CoV-2 lineages, treatment with a mAb cannot achieve viral clearance, but instead represents additional selective immune pressure that can introduce extra mutations. In addition to inefficacy, wasted money and potential side effects, administration of anti-Spike mAbs to basally resistant SARS-CoV-2 lineages should be avoided.

Treatment-emergent resistance after high, safe doses of anti-Spike mAb was soon recognized as a challenge,[61] but the sudden emergence of baseline resistance with novel SARS-CoV-2 variants was largely unexpected (Table 2). The unprecedented evolution rates of the SARS-CoV-2 Spike protein (both at the mAb binding site and at side domains) show how difficult it is for mAb development to keep the pace of natural selection, which is further complicated by time-consuming regulatory steps.

Nevertheless, the consistent observations of convergent evolution[77,78] and yo-yo mutations[79] represent an unexploited opportunity. For example, the current failure of sipavibart could have been anticipated by looking at the increase in prevalence of F456L-harboring variants while the drug was proceeding along the final phases of clinical development. In a prospective manner, the combination of in vitro sensitivity results[80] with genomic sequencing and surveillance[81] could streamline the future anti-Spike mAb pipeline and minimize failures to manufacturers.[82] In times when waves are heterogenous in nature, and no longer dominated by a single variant of concern, automated online tools have been developed to facilitate the almost real-time study of convergent evolution.[83]

Table 2 reports the in vitro efficacy of recently authorized anti-Spike mAbs against SARS-CoV-2 lineages circulating in 2024–2025. After the emergence of universal Evusheld® resistance,[84] only sotrovimab remained partly effective in 2023,[85] and the pipeline[86] is now very limited to Invivyd's pemivibart and AstraZeneca's sipavibart.[87] Pemivibart was granted emergency use authorization (EUA) by the FDA on March 22, 2024 on the basis of immunobridging, while the results of the company-sponsored CANOPY RCT were pre-published on November 17, 2024.[88] None of the 2 drugs have yet been authorized by EMA. Aerium Sinovac's SA-55, the most resilient of the anti-Spike mAb's available to date, remains confined to China.[89] It is clear from the IC_{50} that even mAbs released in 2024 based on the clinical trials run in 2023 are no longer effective against variants circulating in 2025, which has led FDA to restrict pemivibart based on sensitive variants.[90] Several considerations apply to the development of anti-Spike mAbs effective against evolving viral variants,[91] including the ongoing retargeting of Spike evolution at the N-terminal domain.[92]

Combining Anti-Spike mAbs with Other Antivirals

Even without the occurrence of treatment-emerging resistance, the occurrence of very high basal SARS-CoV-2 viral loads in IC patients could easily saturate even the high dose of anti-Spike mAb that are administered. There is then a clear rationale for combining different antiviral mechanisms of actions in order to both reduce viral loads and clear resistant viral quasi-species. To date, no combination of different antiviral therapies has been formally investigated in RCTs in IC COVID-19 patients. Consequently, any inferences and recommendations must rely exclusively on anecdotal evidences or small case series.[93] This is clearly a suboptimal level of evidence, although biological plausibility suggests clear superiority of combination therapies over monotherapies: mAb monotherapies should then be discouraged in IC patients. Nevertheless, it should also be noted that concomitant treatment-emergent resistance to anti-Spike mAb and small molecule antiviral has been reported.[50]

In contrast to therapy, pre-exposure prophylaxis has to defeat only low infecting viral loads, and hence is generally able to achieve viral saturation.

Rescuing Treatment-Emergent mAb Resistance

Managing treatment-emergent anti-Spike mAb resistance in IC patients represents a major challenge. In fact, while many such frail patients cannot tolerate combinations of small molecule antivirals because of their contraindications and side effects, their performance status is likely deteriorated at the time treatment-emergent anti-Spike mAb resistance is diagnosed. Hence, tolerable treatments are needed. In this setting, CCP has shown the ability to rescue anti-Spike mAb failures in IC patients[18,31] and remains the treatment for which the highest level of evidence (ie, RCTs) is available about efficacy specifically in IC patients.[6,7] As biologically plausible, the polyclonality within CCP is able to cope with the SARS-CoV-2 quasi-species swarm.

In settings where CCP is not available, combining antivirals with different mechanisms of actions remains a logical approach, but it should be noted that the prolonged in vivo half-life of IgG mAbs (3–4 weeks) makes emergence of mutations possible as soon as short half-life small molecule antivirals are discontinued:[51] such half-life mismatch is hard to reconcile, given the toxicity associated with prolonged administration of small-molecule antivirals.

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Table 2 In Vitro Efficacy (IC_{50}) of Novel Anti-Spike Monoclonal Antibodies Against SARS-CoV-2 Omicron Lineages Circulating in 2024. When the Unit of Measurement Is Not Specified It Means ng/mL, Followed by the Related Reference. When Exact IC_{50} Has Not Been Disclosed, "=" Means Preserved Efficacy; "-" Means No Data Released yet

Pangolin name	NextStrain name	Sotrovimab/S-309 (Xevudy®)	AZD7442 (Evusheld®)	AZD5156		SA55 (BD55-5514)	VYD222/Pemivibart (Pemgarda®)
			Tixagevimab /AZD8895/ COV2-2196	Cilgavimab /AZD1061/ COV2-2130	AZD3152/ Sipavibart		
BA.2.86 ("Pirola")	23I	–	>2600[62]	>4200[62]	2.8[64]	–	=[66]
			>10000[63]	>10000[63]	4 [65] ^		
BA.2.86.1	–	–	>10000[67]	>10000[67]	–	–	–
JN.1	24A	>120[68]	–	–	29[65] ^	3[69,70]	=[71], 160,[72] 96[70]
JN.1.1	–	No activity[73]	–	–	118[73]	6 [73]	1136[73]
LB.1	–	No activity[73]	–	–	No activity[73]	11 [73]	9297[73]
						7 [69]	400[72]
KP.1.1	–	–	–	–	No activity[73]	7 [73]	2950[73]
KP.2	–	>120[68]	–	–	–	2,[69] 3 [70]	130,[72] 121[70]
KP.2.3	24G	–	–	–	–	5[69]	1260,[72] 651[69]
KP.3	24C	No activity[73]	–	–	No activity[73]	3[69,73]	3668[73]
						2[70,74]	1060[72]
							415[70]
							223[74]
KP.3.1.1	24E	–	–	–	–	6[69]	2675[70]
						0,6[74]	4000[72]
						3[70]	239[74]
XEC	24F	–	–	–	–	5[69]	1753[70]
						3[70]	55 [75]
						9[75]	

LF.7	24H	–	–	–	–	37[75] 16[76]	46 [75]
LF.7.2.1	–	–	–	–	–	31[75]	65[75]
LF.7.9	–	–	–	–	–	13[76]	–
MC.10.1	–	–	–	–	–	17[75]	300[75]
NP.1	–	–	–	–	–	19[75]	230[75]
LP.8.1	–	–	–	–	–	4[75]	24 [75]
LP.8.1.1	–	–	–	–	–	4[76]	–
XEC.25.1	–	–	–	–	–	24[76]	–
BA.3	–	–	–	–	–	29[76]	–
BA.3.2	–	–	–	–	–	58[76]	–
XFH	–	–	–	–	–	31[76]	–
XFG	–	–	–	–	–	9	–
NB.1.8.1 ("Nimbus")	–	–	–	–	–	7[76]	–

Notes: ^ = data for Omi-42, the AZD3152 parent.

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Conclusions

It is strongly recommended that physicians not prescribe anti-Spike mAb monotherapies to IC patients with COVID-19 who are likely to harbor a large viral burden ripe for the selection of mAb-resistant variants. In contrast, viral loads at the beginning of infection are generally low and single mAbs can be successful for pre-exposure prophylaxis. The high viral loads associated with COVID-19 in IC individuals pose a major therapeutic challenge. They are best treated with polyclonal immunoglobulins found in CCP, possibly in combination with small molecule antivirals, with the caveat that this recommendation is based primarily on biological plausibility since there is scant clinical data on the efficacy of these drugs in IC patients, either alone or in combination.

Abbreviations

CCP, COVID-19 convalescent plasma; IC, immunocompromised; mAb, monoclonal antibody; RCT, randomized controlled trial.

Author Contributions

D.F. manuscript writing – original draft, conceptualization; A.C., F.M. and M.F. supervision; manuscript writing – final version.

Disclosure

A.C. serves on the advisory board of and reports stock option from SAB Biotherapeutics. All the other authors declare they have no conflicts of interest to disclose related to this manuscript.

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