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Monoclonal antibody therapies against SARS-CoV-2

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Monoclonal antibodies (mAbs) targeting the spike protein of SARS-CoV-2 have been widely used in the ongoing COVID-19 pandemic. In this paper, we review the properties of mAbs and their effect as therapeutics in the pandemic, including structural classification, outcomes in clinical trials that led to the authorisation of mAbs, and baseline and treatment-emergent immune escape. We show how the omicron (B.1.1.529) variant of concern has reset treatment strategies so far, discuss future developments that could lead to improved outcomes, and report the intrinsic limitations of using mAbs as therapeutic agents.

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Introduction

The first monoclonal antibody (mAb) for clinical use (muromonab-CD3) was approved by the US Food and Drug Administration (FDA) in 1986.[1] Since then, about ten new mAbs have been approved each year (mostly IgG1), with an estimated global yearly sale of US$75 billion in 2021.[2] Most of these mAbs have been licensed for non-infectious disease indications. However, successful efforts have been made in the COVID-19 pandemic to research and develop mAbs against SARS-CoV-2. At the beginning of the COVID-19 pandemic, IgG mAbs against the spike protein of SARS-CoV-2, either as single agents or mAb cocktails (ie, a combination of two or more mAbs), were announced and advertised by many authorities as the most effective antibody therapeutic solution for COVID-19.[3] As of March 4, 2022, the Coronavirus Antibody Database (CoV-AbDab) contains 5210 antibodies and nanobodies against SARS-CoV, MERS-CoV, and SARS-CoV-2.

Many randomised clinical trials of mAb therapy and prophylaxis have been launched, initially for patients being treated in hospital and then for outpatients, all showing overall moderate efficacy and good safety (tables 1, 2). Many classifications of anti-spike mAbs according to the targeted epitopes have been suggested (table 3). In this paper, we review the information available for mAbs against SARS-CoV-2 (panel 1) to identify the strengths and weaknesses of this therapeutic strategy, which are apparent from 2 years of clinical experience.

Efficacy in randomised clinical trials

Efficacy of mAbs was measured as reduction of infection rates when mAbs were used in pre-exposure or post-exposure prophylaxis, reduction in hospital admissions when mAbs were administered as treatment for outpatients, or reduction in disease progression or mortality when mAbs were used as treatment for inpatients. Similar to therapies based on neutralising antibodies, such as the cheaper COVID-19 convalescent plasma, therapeutic efficacy was exclusively shown in seronegative and early inpatients. Reductions of the measured variables ranged between 30% and 40%, which was enough to meet statistical significance, but the effect was not sufficiently large for these mAbs to be considered an effective therapy, since a substantial proportion of patients treated with mAbs did not appear to benefit. Better results were observed for prophylactic indications and in outpatients, especially when patients at high risk of disease progression were recruited to increase the cost-effectiveness of the procedure.

Specifically, a randomised clinical trial that led to the authorisation of bamlanivimab (Eli Lilly, Indianapolis, IN, USA) showed that the efficacy of bamlanivimab administered alone was not significant: the proportion of patients who recovered in, or were discharged from, hospital ranged from 82% to 88% for the bamlanivimab group versus 79% to 90% for the placebo group.[5] REGN-COV2 (a cocktail of two mAbs, casirivimab and imdevimab; Regeneron and Roche, New York, NY, USA) use led to an 84–92% relative risk reduction in developing symptomatic COVID-19 infections, and a significant reduction in mortality in patients treated in hospital at day 28 from baseline.[7] Sotrovimab (GSK, Brentford, UK) use led to a relative risk reduction of 85% in progression of the infection leading to admission to hospital or death.

	FDA	EMA
Bamlanivimab	EUA Nov 9, 2020, for early therapy in outpatients at high risk of disease progression; revoked on April 15, 2021	Not authorised
Bamlanivimab and etesevimab	EUA Feb 9, 2021, for early therapy in outpatients at high risk of disease progression; restricted on Jan 24, 2022	Marketing authorisation granted on March 11, 2021, for early therapy in outpatients at risk of disease progression; withdrawn by Eli Lilly on Oct 29, 2021
Casirivimab and imdevimab	EUA Nov 21, 2021, for early therapy in outpatients at high risk of disease progression; restricted on Jan 24, 2022	Marketing authorisation granted on Nov 12, 2021, for early therapy in outpatients at risk of disease progression and post-exposure prophylaxis
Tixagevimab and cilgavimab	EUA Dec 8, 2021, for pre-exposure prophylaxis	In rolling review
Sotrovimab	EUA May 26, 2021, for early therapy in outpatients at high risk of disease progression; withdrawn on April 5, 2022	Marketing authorisation granted on Dec 17, 2021, for early therapy in outpatients at risk of disease progression
Regdanvimab	Not approved yet	Marketing authorisation granted on Nov 12, 2021, for early therapy in outpatients at risk of disease progression
Bebtelovimab	EUA Feb 11, 2022, for early therapy in outpatients at high risk of disease progression	Not authorised
Damubarvimab and romlusevimab	Not authorised	Not authorised

EMA=European Medicines Agency. EUA=emergency use authorisation. FDA=US Food and Drug Administration.

Table 1: **Authorisation status for selected monoclonal antibodies by the FDA and EMA**

	Location	Date of recruitment	Treatment group (n)	Control group (n)	Main efficacy outcomes
Bamlanivimab					
Gottlieb et al (2021)[4]	USA and Puerto Rico	June 17–Aug 21, 2020	Three groups with different doses: 700 mg (n=101), 2800 mg (n=107), and 7000 mg (n=101)	Placebo (n=156)	(1) The change from baseline to day 29 in viral load AUC was significant for the 2800 mg dose group (difference −9·50 [95% CI −16·32 to −2·68]; p=0·006) compared with the placebo group; (2) the change in symptom improvement from baseline to day 11 was significant for the 700 mg dose group (difference 16·0% [95% CI 3·6–28·4]; p=0·02) and the 7000 mg dose group (15·0% [2·6–27·4]; p=0·02) compared with the placebo group; (3) the change from baseline to day 29 in the proportion of patients with COVID-19-related hospitalisation or emergency department admission was not significant for any treatment group compared with the placebo group; and (4) no deaths during the study
ACTIV-3/TICO LY-CoV555 Study Group et al (2021)[5]	USA, Argentina, Denmark, Georgia, Greece, India, Mexico, Mozambique, Nigeria, Poland, Singapore, Spain, Switzerland, Ukraine, and UK	Aug 5–Oct 13, 2020	n=163	Placebo (n=151)	(1) 82% of the patients in the treatment group had a sustained recovery *vs* 79% in the placebo group; (2) 88% of the patients in the treatment group had a hospital discharge *vs* 90% in the placebo group; and (3) nine patients in the treatment group died *vs* five in the placebo group; of these 14 deaths, 12 were attributed to worsening of COVID-19 and two to cardiopulmonary arrest
Bamlanivimab and etesevimab					
Gottlieb et al (2021)[4]	USA and Puerto Rico	Aug 22–Sept 3, 2020	n=112	Placebo (n=156)	(1) The change from baseline to day 11 in viral load AUC was significant for the treatment group (difference −0·57 [95% CI −1·00 to −0·14]; p=0·01) compared with the placebo group; (2) the change from baseline to day 29 in viral load AUC was significant for the treatment group (difference −17·91 [95% CI −25·25 to −10·58]; p<0·001) compared with the placebo group; (3) the change in symptom improvement from baseline to day 11 was not significant compared with the placebo group; (4) the proportion of patients with COVID-19-related hospitalisation or emergency department admission at day 29 was 0·9% in the treatment group *vs* 5·8% in the placebo group, with the difference between groups being significant (difference −4·9% [95% CI −8·9 to −0·8]; p=0·049); and (5) no deaths during the study
Casirivimab and imdevimab					
Weinreich et al (2021)[6]	USA, Mexico, and Romania	June 16–Aug 13, 2020	Three groups with different doses: 1200 mg (n=736), 2400 mg (n=1355), and 8000 mg (n=625)	Placebo (n=1341)	(1) In the full analysis set, 3% of patients in the treatment groups reported at least one medically attended visit, compared with 6% in the placebo group; (2) in the serum antibody-negative subgroup, 15% of patients had a medically attended visit, compared with 6% in the placebo group; and (3) mean difference in viral load from baseline to day 7 was −0·71 $\log_{10}$ copies per mL (95% CI −0·90 to −0·53) for the 1200 mg dose group and −0·86 $\log_{10}$ copies per mL (−1·00 to −0·72) for the 2400 mg dose group compared with the placebo group
Isa et al (2021)[7]	USA	Not reported	n=729	Placebo (n=240)	(1) 92·4% reduction in relative risk of developing symptomatic COVID-19 and 100% risk reduction for SARS-CoV-2 seroconversion (anti-nucleocapsid IgG) in the treatment group compared with the placebo group; (2) no patient in the treatment subgroup of seronegative patients at baseline (n=617) was seropositive at the end of the study *vs* 20 patients in the placebo seronegative subgroup (n=208); and (3) no deaths during the study
O'Brien et al (2021)[8]	USA, Moldova, and Romania	Not reported	n=753	Placebo (n=752)	(1) 84% reduction in relative risk of developing symptomatic COVID-19 in the treatment group compared with the placebo group; (2) in the overall population, the mAb cocktail prevented symptomatic and asymptomatic infections; and (3) the median time to resolution of symptoms and the duration of a high viral load was 2 weeks shorter in the treatment group than in the placebo group
RECOVERY Collaborative Group (2022)[9]	UK	Sept 18, 2020–May 22, 2021	n=4839	Best standard of care (n=4946)	(1) Significant reduction in mortality at day 28 (relative risk 0·80 [95% CI 0·70–0·91]) for COVID-19 hospitalised patients (seronegative for SARS-CoV-2 on admission to hospital) treated with the mAb cocktail; and (2) in the subgroup of patients who were seronegative for SARS-CoV-2 and not on ventilation at baseline, patients in the treatment group had a less frequent progression to use of ventilation than patients in the control group, although this finding was not observed in the overall population

(Table 2 continues on next page)

Regdanvimab (Celltrion, Incheon, South Korea) use reduced the risk of admission to hospital or death by 72% in patients at high risk of progression to severe COVID-19, and only few patients with symptomatic infection required admission to hospital or oxygen therapy, or died.[13] Bebtelovimab (Eli Lilly, Indianapolis, IN, USA) was approved in patients with mild-to-moderate COVID-19 at high and low risk of disease progression, either administered alone or together with bamlanivimab and etesevimab (Eli Lilly, Indianapolis, IN, USA). In the overall population treated with bebtelovimab alone or the mAb cocktail, a small proportion of patients (1·7–4·0%) required admission to hospital or died.[56] AZD7442 (a cocktail of tixagevimab and cilgavimab; AstraZeneca,

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	Location	Date of recruitment	Treatment group (n)	Control group (n)	Main efficacy outcomes
(Continued from previous page)					
Tixagevimab and cilgavimab					
Levin et al (2022)[10]	USA, Belgium, France, Spain, and UK	Nov 21, 2020–March 22, 2021	n=3460	Placebo (n=1737)	In the primary efficacy analysis, patients treated with the mAb cocktail had a 76·7% reduction (95% CI 46·0–90·0; p<0·001) in relative risk of developing symptomatic COVID-19 compared with the placebo group; the risk reduction was 82·8% at 6 months (65·8–91·4; p value not available)
AstraZeneca (2021)[11]	USA and UK	Not reported	n=749	Placebo (n=372)	(1) No significant reduction in the risk of developing symptomatic COVID-19 in the overall population; (2) in the pre-planned subgroup analysis, risk of developing symptomatic COVID-19 was reduced by 73% (95% CI 27–90) in the treatment subgroup of patients who were PCR-negative at time of dosing compared with the placebo group; and (3) in the post-hoc subgroup analysis, risk of developing symptomatic COVID-19 was reduced by 92% (32–99) in the treatment subgroup of patients who were PCR-negative at baseline with follow-up for >7 days after dosing compared with the placebo group
AstraZeneca (2021)[12]	USA, Argentina, Brazil, Czech Republic, Germany, Hungary, Italy, Japan, Mexico, Peru, Poland, Russia, Ukraine, Spain, and UK	Not reported	n=407	Placebo (n=415)	(1) Risk of progression to severe COVID-19 or death was 4·4% in the treatment group (outpatients within 8 days from symptom onset) at day 29 compared with 8·9% in the placebo group (ie, 50% relative risk reduction); and (2) risk of progression to severe COVID-19 or death was 3·5% in the treatment subgroup of patients who received treatment within 5 days from symptom onset compared with 10·7% in the placebo group
Sotrovimab					
Gupta et al (2021)[13]	USA, Austria, Brazil, Canada, Peru, Spain, and UK	Jan 19–Feb 17, 2021	n=291	Placebo (n=292)	(1) 1% of patients in the treatment group, compared with 7% in the placebo group, had disease progression leading to admission to hospital for any cause, or death (relative risk reduction 85% [97·24% CI 44–96]; p=0·002); and (2) one patient in the placebo group died
Regdanvimab					
Kim et al (2021)[14]	South Korea	Dec 16, 2020–March 1, 2021	Phase 1; four groups with different doses in study 1.1: 10 mg/kg (n=6); 20 mg/kg (n=6), 40 mg/kg (n=6), and 80 mg/kg (n=6); three groups with different doses in study 1.2: 20 mg/kg (n=5), 40 mg/kg (n=5), and 80 mg/kg (n=5)	Placebo (n=8 in study 1.1; n=3 in study 1.2)	(1) The mean reduction in viral titres in nasopharyngeal swabs from baseline to day 14 was greater for patients in the treatment groups compared with patients in the placebo group; and (2) all patients (except one in the placebo group) recovered from COVID-19 at day 14 with a shorter mean time to recovery (3·39 days for patients in the treatment groups *vs* 5·25 days in the placebo group)
Eom et al (2021)[15]	South Korea	Oct 7–Dec 18, 2020	Phase 2; two groups with different doses: 40 mg/kg (n=105) and 80 mg/kg (n=111)	Placebo (n=111)	(1) Median time from receiving a positive RT-qPCR test result to a negative one was 12·75 days for patients in the 40 mg/kg dose group and 11·89 days in the 80 mg/kg dose group, compared with 12·94 days in the placebo group; (2) 4·0% of patients in the 40 mg/kg dose group and 4·9% in the 80 mg/kg dose group required admission to hospital or oxygen therapy from baseline to day 28, compared with 8·7% in the placebo group; and (3) no deaths during the study
Celltrion Healthcare (2021)[16]	South Korea	Not reported	Phase 3 (n=undisclosed)	Placebo (n=undisclosed)	(1) Total of 1315 patients at risk for severe COVID-19—at day 28, patients in the treatment group had a 72% reduction in risk of hospitalisation or death compared with the placebo group (3·1% *vs* 11·1%; p<0·0001); and (2) no deaths during the study

(Table 2 continues on next page)

	Location	Date of recruitment	Treatment group (n)	Control group (n)	Main efficacy outcomes
(Continued from previous page)					
Bebtelovimab					
Dougan et al (2022)[17]	USA, Argentina, and Puerto Rico	Not reported	Bebtelovimab (n=125); bebtelovimab plus bamlanivimab and etesevimab (n=127)	Placebo (n=128)	(1) Low-risk patients (based on the Centers for Disease Control and Prevention guidance[18]): 14% of patients receiving treatment with bebtelovimab and 13% of patients receiving treatment with the combination of mAbs had a persistently high viral load at day 7; and (2) median time to symptom resolution ranged from 6 to 7 days for patients in the treatment group *vs* 8 days in the placebo group
Dougan et al (2022)[17]	As above	As above	Bebtelovimab (n=100); bebtelovimab plus bamlanivimab and etesevimab (n=50)	As above	High-risk patients (based on the Centers for Disease Control and Prevention guidance[18]): 3% of patients receiving treatment with bebtelovimab were hospitalised or died because of COVID-19, compared with 4% of patients receiving treatment with the combination of mAbs
Dougan et al (2022)[17]	As above	As above	Bebtelovimab plus bamlanivimab and etesevimab (n=176)	As above	(1) High-risk patients (based on the Centers for Disease Control and Prevention guidance[18]): COVID-19-related hospitalisations were reported for 1·7% of patients; and (2) no deaths during the study
Damubarvimab and romlusevimab					
ACTIV-3/TICO Study Group (2022)[19]	USA, Argentina, Denmark, Georgia, Greece, India, Mexico, Mozambique, Nigeria, Poland, Singapore, Spain, Switzerland, Ukraine, and UK	Dec 16, 2020–March 1, 2021	n=176	Placebo (n=178)	(1) 45% of patients in the treatment group and 51% in the placebo group had an improvement in the seven-category pulmonary ordinal scale from baseline to day 5; and (2) the adjusted odds ratio (active treatment *vs* placebo) for patients being in a more favourable category on the pulmonary scale on day 5 was 0·98 (95% CI 0·67–1·43)

AUC=area under the receiver operating characteristic curve. mAb=monoclonal antibody. TICO=Therapeutics for Inpatients with COVID-19.

Table 2: **Efficacy of anti-spike mAbs approved so far for clinical use in randomised clinical trials**

Cambridge, UK) is the only combination approved by the FDA for pre-exposure prophylaxis: among patients who had a negative SARS-CoV-2 PCR test at baseline, tixagevimab and cilgavimab reduced the risk of developing symptomatic COVID-19 by 73–92%, and the risk of disease progression or death ranged from 3·5% to 4·4%.[11]

Unfortunately, no randomised clinical trial was done by a pharmaceutical company after vaccine coverage was high, and thus mAbs continued to be administered to individuals with vaccine-induced seropositivity, without any conclusive evidence supporting their efficacy in these settings. Such lack of reappraisal by public investigators is a serious concern for reliability of current evidence on mAbs. However, mAb efficacy in individuals with vaccine-induced seropositivity is likely to be much lower than in individuals who are not vaccinated: novel randomised clinical trials are hence needed to support the assessment of cost versus efficacy of the intervention in this group of individuals, who represent most people nowadays.

Notably, when poor results were observed for patients who were treated in hospital, pharmaceutical research moved to establishing efficacy of, and using, mAbs in outpatients, for whom mAbs were more likely to be effective on the basis of previous experience with antiviral mAbs. These mAb trials had an advantage compared with randomised clinical trials of COVID-19 convalescent plasma because they were sponsored by pharmaceutical companies; trials of COVID-19 convalescent plasma, in which efficacy was likely to be low and there were not as many outpatients, were instead supported by physicians and the medical community to assist patients with advanced disease.[57]

The rapid development of the pandemic highlighted some predictable limitations in the development of mAb therapies: of a very broad pipeline,[58] only a few candidates were initially approved by regulatory authorities in sufficient time to be used. The initial success of some mAbs, such as casirivimab and imdevimab, discouraged small companies from pursuing other research and development efforts, because of the assumption that the mAbs that had reached the market first would have been adequate and sufficient therapeutics. With the emergence of the delta (B.1.617.2) and omicron (B.1.1.529) variants of SARS-CoV-2, the mAbs that were used early in the pandemic against the wild-type and alpha (B.1.1.7) variants lost their neutralising activity. Therefore, when other mAbs were needed, manufacturing bottlenecks largely hindered large-scale deployment.[59] However, even if additional mAbs had been widely available, their cost would have probably remained prohibitive even for high-income countries. Notably, when mAbs were ultimately made available, many did not show to be effective against SARS-CoV-2 within a short time after their introduction, because the virus rapidly escaped their narrow specificity with the generation of mAb-resistant variants.[60]

Safety in randomised clinical trials

The safety of mAbs was measured as the number of adverse events and serious adverse events occurring after their administration. Generally, adverse events were non-severe (eg, diarrhoea and nausea) and self-limiting. The most common adverse events were injection-site reactions, headache, chills, and bronchospasm.[4,6,8–10,12,19] Serious adverse events occurred very rarely,[4,6,8–10,12,19] and those affecting the respiratory tract (eg, shortness of breath) were probably related to the progression of COVID-19. Death occurred only in few patients, especially those clinically at high risk of disease progression or treated in hospital. More than 95% of patients completed the infusion of mAbs. The incidence of antidrug antibodies was assessed only in the regdanvimab trial,[61] in which they were not detected. Nevertheless, repeated exposure to mAbs, such as in pre-exposure prophylaxis, comes with concerns, such as a growing incidence of treatment-emergent resistance.

Resistance to mAbs

As for any other therapeutic, resistance to mAbs binding the spike protein can be either initial (ie, pre-existing before treatment) or treatment-emergent (ie, positive selection of immune-escape variants after treatment). Both types of resistance can be predicted in vitro, using gene sequencing efforts for initial resistance, or viral serial passage in the presence of the mAb for treatment-emergent resistance. However, the implications of these types of resistance are different. Initial resistance discourages regulatory bodies from introducing a mAb into therapeutic guidelines, when the prevalence of the mutations that confer initial resistance to the mAb in the circulating strains is high. By contrast, a high incidence of treatment-emergent resistance could trigger a mandate follow-up order to promptly detect immune escape and treatment failure. With regard to viral fitness, although widespread circulation of a resistant strain invariably indicates enhanced fitness, typically only a few mutations associated with treatment-emergent resistance are sufficiently fit to spread within communities. This reduced viral fitness is clearly shown by the relative scarcity of SARS-CoV-2 lineages with E406 mutations that are resistant to REGN-COV2 in the Global Initiative on Sharing All Influenza Data (GISAID). In addition to REGN-COV2, the spike E406W mutation abrogates neutralisation mediated by cilgavimab. E406W results in allosteric changes to the ACE2-binding site, thereby reducing receptor recognition by these three mAbs.[62] On the other hand, sudden emergence of the Q493R mutation in the omicron variant of concern, which is resistant to bamlanivimab, cannot be imputed as immune escape, since the omicron variant emerged many months after the use of bamlanivimab was discontinued worldwide.[63]

The in-vitro studies that have investigated spike mutations in variants of interest and variants of concern conferring resistance to mAbs are summarised in

	Protein Data Bank identification code	Finkelstein et al (2021)[20] classification	Barnes et al (2020)[21] classification	Yuan et al (2021)[22] classification
4A8	7c2l	NTD binding	..	..
CC12.3	6xc4	RBM class I	Class 1	RBS-A
C105	6xcm	RBM class I	Class 1	RBS-A
P2G3[23]	7qtg (held for release)	..	..	..
553-49[24]	7wog (held for release)	..	..	..
B38	7bz5	RBM class I	Class 1	RBS-A
C102	7k8m	RBM class I	Class 1	..
COVA2-39	7jmp	RBM class I	Class 2	RBS-B
CC12.1	6xc2	RBM class I	..	RBS-A
Casirivimab	6xdg	RBM class I	..	..
CV30	6xe1	RBM class I	..	RBS-A
CV07-250	6xkq	RBM class I	..	RBS-B
BD-604	7ch4	RBM class I	..	RBS-A
BD-629	7ch5	RBM class I	..	RBS-A
BD-236	7chb	RBM class I	..	RBS-A
COVA2-04	7jmo	RBM class I	..	RBS-A
Etesevimab	7c01	RBM class I	..	RBS-A
S2H14[25]	7jx3	RBM class I	..	..
S2E12[26]	7k4n	RBM class I	..	..
Amubarvimab	7cdi	RBM class I*	..	..
COR-101 or STE90-C11[27]	7b3o	RBM class I*	..	..
87G7[28]	7r40	RBM class I*	..	..
CV07-287[29]	7s5p, 7S5q, or 7s5r (held for publication)	RBM class I*	..	..
P5C3[30]	7p40 or 7phg	RBM class I*	..	..
S2K146[31]	7tas or 7tat	RBM class I*	..	..
CV07-270	6xkp	RBM class II	..	RBS-C
P2B-2F6	7bwj	RBM class II	Class 2	RBS-C
C002	7k8s	RBM class II	Class 2	..
C104	7k8u	RBM class II	Class 2	..
C119	7k8w	RBM class II	Class 2	..
C121	7k8x	RBM class II	Class 2	..
H11-D4	6yz5	RBM class II	..	..
H11-H4	6zhd	RBM class II	..	..
Sb23	7a29	RBM class II	..	..
BD-368-2	7che or 7chc	RBM class II	..	RBS-C
S2H13[25]	7jv2	RBM class II	..	..
Ty1	6zxn	RBM class II	..	..
5A6	7m71	RBM class II*	..	..
Cilgavimab	7l7e	RBM class II*	..	..
P17[32]	7cwo	RBM class II*	..	..
Ab2-4	6xey	RBM class III	Class 2	RBS-B
BD-23	7byr	RBM class III	Class 2	RBS-B
C144	7k90	RBM class III	Class 2	..
Nb20	7jwb	RBM class III	..	..
S2M11[26]	7k43	RBM class III	..	..
Nb6	7kkk	RBM class III	..	..
Bamlanivimab	7kmg	RBM class III*	..	..

(Table 3 continues on next page)

	Protein Data Bank identification code	Finkelstein et al (2021)[20] classification	Barnes et al (2020)[21] classification	Yuan et al (2021)[22] classification
(Continued from previous page)				
Tixagevimab	7l7d	RBM class III*	..	..
S2D106[33]	7r7n	RBM class III*	..	..
Regdanvimab	7cm4	RBM class III*	..	..
MW33 or MW05[34]	7dk0	RBM class II*	..	..
S309 and the LS-modified sotrovimab[25,35]	6wps	RBD core cluster I	Class 3	S309 epitope
Imdevimab	6xdg	RBD core cluster I	Class 3	..
C110	7k8v	RBD core cluster I	Class 3	..
C135	7k8z	RBD core cluster I	Class 3	..
47D11[36]	7akd	RBD core cluster I*	..	..
BG10-19[37]	7m6e	RBD core cluster I*	..	..
Bebtelovimab	7mmo	RBD core cluster I*	..	..
CR3022	6w41	RBD core cluster II	Class 4	CR3022 epitope
EY6A	6zcz	RBD core cluster II	Class 4	CR3022 epitope
ADG-2[38] and its half-life engineered version adintrevimab[39]	No structure found on SAbDab	..	..	CR3022 epitope*
S2A4	7jvc	RBD core cluster II	Class 4	..
S304[25,35]	7jw0	RBD core cluster II	Class 4	..
VHH-72	6waq	RBD core cluster II	..	..
H014[32]	7cah	RBD core cluster II	..	..
VHH72	6waq	RBD core cluster II	..	..
DH1047	7sg4	RBD core cluster II*	..	..
S2X259[40]	7m7w	RBD core cluster II*	..	..
MW06[34]	7dpm	RBD core cluster II*	..	..
S2H97[33]	7m7w	RBD core cluster II*	..	..
COVA1-16	7jmw	..	Class 4	CR3022 epitope
7D6[41]	7eam	Novel RBD core binding epitope*	..	..
6D6[41]	7ean	Novel RBD core binding epitope*	..	..
CC40.8[42]	7sjs	S2 stem-helix epitope*	..	..
S2P6[43]	7rnj	S2 stem-helix epitope*	..	..
1249A8[44]	..	S2 stem-helix epitope*	..	..

The classification into clusters by Brouwer and colleagues[45] is not included here because the authors only deposited electron microscopy data to the EMDB (https://www.ebi.ac.uk/emdb/), but did not deposit structural information to the Protein Data Bank (https://www.rcsb.org/). Monoclonal antibodies without a solved structure (ie, with no Protein Data Bank entry) are: 8G3,[46] upanovimab (SCTA01),[47] 4-19,[48] 2-17,[48] 910-30,[49] S2X58,[33] 1-20,[48] 4-18,[48] 5-7,[48] 5-24,[48] 2-7,[48] P2C-1A3,[50] 2-15,[48] ABP-310,[51] VacW-209,[52] STI-9167,[53] 10-40,[54] and TY027 (NCT04649515; terminated due to low recruitment rate). An EMDB entry is available for S2X35,[25] 2-36,[48] 2-43,[48] and 4-8.[48] EMDB=Electron Microscopy Data Bank. RBD=receptor-binding domain. RBM=receptor-binding motif. SAbDab=Structural Antibody Database.
*Antibodies were not included in the original authors' classification, but binned into Finkelstein categories retrospectively by matching epitopes and approach angles to members of the original clusters.

Table 3: **Competition clusters for anti-SARS-CoV-2 spike monoclonal antibodies according to three different classification schemes**

For more on **GISAID** see https://www.gisaid.org/epiflu-applications/covsurver-mutations-app/

panel 2. Caution should be used when drawing conclusions on these complex variants: for example, the delta variant of concern consists of more than 200 sublineages, many of which harbour spike mutations that could affect mAb sensitivity of individual sublineages.[74] The reduction of mAb neutralising activity by different circulating variants of interest and variants of concern of SARS-CoV-2 is shown in table 4.

We previously reviewed immune escape to therapeutics based on neutralising antibodies, including mAbs,[63] and we provide an update of our previous research as of Feb 15, 2022, in the appendix (pp 1–6).

The omicron hurricane

In November, 2021, omicron emerged, a new variant of concern that led to an unexpected change in the pandemic, due to its high reproduction number and ability to cause breakthrough infections in vaccinated individuals. Because of omicron's high number of spike mutations and deletions compared with previous variants of concern, most clinically approved mAbs suddenly lost their efficacy against SARS-CoV-2 (appendix pp 1–6).[114] The FDA was among the first regulatory authority to issue updated guidance documents on mAbs; on Jan 24, 2022, the FDA revised the authorisations for two mAb treatments—REGN-COV2, and a cocktail of bamlanivimab and etesevimab—to limit their use to patients who are likely to have been infected with, or exposed to, a variant that is susceptible to these treatments.[115] Attributing infection to a specific variant requires sequencing efforts, which are expensive and poorly scalable, and the long turnaround time is not compatible with early administration of mAbs to seronegative patients. When omicron emerged, only sotrovimab retained in-vitro efficacy; however, because sotrovimab is a single mAb rather than a cocktail, it is susceptible to the emergence of immune-escape variants, such as the E340K mutation, which has been reported in up to 10% of recipients of sotrovimab.[116,117] After new omicron sublineages emerged, resistance of the BA.2 sublineage, which is nowadays dominant, was reported:[77,78,89,90,106,118] the FDA first restricted the use of sotrovimab on Feb 25, 2022, and withdrew authorisation on April 5, 2022. Despite losses in neutralisation in vitro, S309 (the parent mAb of sotrovimab) or AZD7442 treatments reduced BA.1, BA.1.1, and BA.2 lung infection in susceptible mice that expressed human ACE2 (K18-hACE2);[119] however, animal models are clearly not enough.

To improve preparedness, the FDA approved bebtelovimab for outpatients on Feb 11, 2022, on the basis of only a phase 2 clinical trial;[120] however, similar to sotrovimab, because bebtelovimab is a single mAb, it is susceptible to the emergence of immune-escape variants. Consequently, in the trial, bebtelovimab was co-administered with etesevimab plus bamlanivimab, representing the first cocktail of three mAbs against SARS-CoV-2.

We previously reviewed the limitations of the bamlanivimab plus etesevimab,[121] and the casirivimab plus imdevimab[122] cocktails, and especially their loss of neutralising activity against the omicron variant of

concern, which is currently the dominant variant worldwide.

Fortunately, all the currently available small molecule antivirals—remdesivir, molnupiravir, and nirmatrelvir—have remained effective in vitro against omicron.[123] However, these antivirals are expensive, moderately effective in vivo,[124] and sometimes come with safety concerns, such as the mutagenicity of molnupiravir to host RNA.[125] Because of the scarcity of antiviral agents, both the FDA[126] and the International Swaps and Derivatives Association[127] also reassessed COVID-19 convalescent plasma for outpatients at risk of progression, because its polyclonal nature makes it less susceptible to immune escape by variants.

Perspectives

Despite the widespread use of mAbs in medicine, relatively few have been developed against viral diseases: among them, palivizumab (AstraZeneca, Cambridge, UK) has been approved for pre-exposure prophylaxis of respiratory syncytial virus in infants at high risk,[128] RAB-1 (Serum Institute of India, Pune, India) for post-exposure prophylaxis of rabies, and the REGN-EB3 cocktail (Regeneron, New York, NY, USA), which is a combination of atoltivimab, maftivimab, and odesivimab, for the treatment of Ebola virus disease.

In contrast to the respiratory viruses that cause systemic infections, such as measles, rubella, varicella, and smallpox (which was declared eradicated by WHO in 1980), the endemic coronaviruses, influenza viruses, respiratory syncytial viruses, parainfluenza viruses, and SARS-CoV-2 primarily infect epithelial cells on mucosal surfaces and generate a reduced systemic immune response, at least initially and in patients who have mild disease. Furthermore, because replication of these viruses occurs in the nostrils, systemic humoral immunity is low such that antibodies specific for viral antigens are not able to always prevent infection. These antibodies thus elicit incomplete and transient protective immunity leading to reinfections. Additionally, systemically administered vaccines elicit systemic responses that are effective at moderating the severity of disease but do not prevent infection.

The coronaviruses pose major challenges because they combine high infectivity and genomic variability that translates into frequent protein changes, resulting in high antigenic variation. Consequently, coronaviruses are hard to eradicate; yet, pandemic preparedness plans include the development of universal vaccines[129] and mAbs targeting shared epitopes among coronaviruses. Furthermore, modern recombinant mAb technology introduces several modifications to the primary sequence to improve or ablate effector functions and increase circulation half-life.[130]

Extending mAb half-life

The fragment crystallisable (Fc) region of immunoglobulin is responsible for its isotype and serum half-life, and for engaging the cellular Fc receptors to promote phagocytosis, complement activation, and antibody-dependent cell cytotoxicity. Hence, the Fc region has received considerable attention in efforts to alter the properties of mAbs to improve pharmacokinetic and effector functions of immunoglobulins. Fc-modified mAbs with the amino acid substitution M252Y/S254T/T256E (YTE; a modification associated with a serum half-life two to four times longer than the unmodified mAbs) were developed for the prophylaxis of respiratory syncytial viruses in infants (eg, nirsevimab [AstraZeneca, Cambridge, UK and Sanofi, Paris, France][131,132]). Additionally, the same technology was used in the development of AZD7442, the anti-SARS-CoV-2 mAb cocktail containing tixagevimab and cilgavimab approved for pre-exposure prophylaxis. mAb half-life can also be expanded with the LS mutation (Met428Leu/Asn434Ser), which does not affect antibody-dependent cell

Panel 1: **List of main anti-spike mAbs and mAb cocktails authorised or in advanced development stages**

Adagio Therapeutics
- Adintrevimab (ADG20)

AstraZeneca
- AZD7442 long-acting antibody (combination of tixagevimab [AZD8895 or COV2-2196] and cilgavimab [AZD1061 or COV2-2130])

Beigene
- BGB-DXP604
- BGB-DXP593

BMS
- C135 (C135-LS if with LS mutation[55])
- C144 (C144-LS if with LS mutation[55])

Brii Biosciences
- Amubarvimab (BRII-196)
- Romlusevimab (BRII-198)

Celltrion
- Regdanvimab (CT-P59)

Eli Lilly (AbCellera and Junshi [ie, original manufacturers before commercial agreements])
- Etesevimab (LyCoV016, CB6, JS016, or LY3832479)
- Bamlanivimab (LY-CoV555 or LY3819253)
- Bebtelovimab (LY-CoV1404 or LY3853113)

Regeneron and Roche
- REGN-COV2 (combination of imdevimab [REGN10987] and casirivimab [REGN10933])

GSK (Vir Biotechnology)
- Sotrovimab (VIR-7831 or GSK-4182136; derived from S309)
- VIR-7832 or GSK-4182137 (derived from S309)

mAb=monoclonal antibody.

See Online for appendix

Panel 2: **Spike mutations associated with resistance in vitro to clinically approved monoclonal antibodies**

Bamlanivimab[64–66]
L452R (>100-fold reduction); E484D/K/Q (>100-fold reduction); G485P; F490S/L (100-fold reduction); Q493R/K (100-fold reduction); and S494P/R (100-fold reduction)

Bebtelovimab[67]
K444Q (>83-fold reduction) and V445A (>83-fold reduction)

Casirivimab[64]
E406W/D (50–93-fold reduction); K417E/N/R/T (25–100-fold reduction); V455T (>100-fold reduction); Y453F (>100-fold reduction); L455F (80-fold reduction); A475R (44-fold reduction); E484K/Q (20–55-fold reduction); F486x; F486K/L/R/S/V (>100-fold reduction); N487R (>100-fold reduction); and Q493E/K/R (25–100-fold reduction)

Cilgavimab[66,68–70]
E484K (3·2-fold reduction)

Etesevimab[64–66]
K417N/T (100-fold reduction); D420N (100-fold reduction); F456R/A/K (100-fold reduction); N460K/S/T/Y (50–100-fold reduction); I472D; A475R/V (20–100-fold reduction); E484K; N487R (100-fold reduction); G485P; and Q493R/K (100-fold reduction)

Imdevimab[64]
E406W (>100-fold reduction); N439K (25–100-fold reduction); N440K (28–96-fold reduction); K444L/M/N/Q/T (>100-fold reduction); V445A (>100-fold reduction); G446V (>100-fold reduction); N450D (9–32-fold reduction); Q498H (17-fold reduction); P499S (>100-fold reduction); and E484K (16-fold reduction)

Regdanvimab[71]
L452R (35-fold reduction); E484K (8·7-fold reduction); and N501Y (5·5-fold reduction)

Sotrovimab[72,73]
P337R/L/H/T (180–276-fold reduction) and E340K/A/G (27–300-fold reduction)

Tixagevimab[66,68–70]
E484K (4–11-fold reduction) and S982A (3·2-fold reduction)

Data are sourced via the Stanford University Coronavirus Antiviral and Resistance Database (accessed online on March 4, 2021, at https://covdb.stanford.edu/search-drdb).

cytotoxicity function.[55,133] This modification was used in the anti-spike mAbs sotrovimab and adintrevimab (Adagio Therapeutics, Waltham, MA, USA),[134] and the C135-LS and C144-LS cocktail (BMS, New York, NY, USA).[55]

Ablation of effector functions

The immunoglobulin Fc region can also be modified to reduce effector functions. Such modifications are desirable in clinical situations in which stimulation of other components of the immune system, such as complement activation or engaging Fc receptors, can trigger side-effects. To reduce the risk of both antibody-dependent enhancement and antibody-dependent cell cytotoxicity, IgG1 Fc regions can be modified to eliminate binding to the Fcγ receptors FcγRI, FcγRIIa, and FcγRIIIa by changing two amino acids in the CH2 domain (L234A/L235A [LALA]). For IgG4, FcγR binding can be abrogated by changing Ser228 to Pro in the hinge region and Leu235 to Glu (SPLE or PE mutations).[135] Changing Pro329 to Glu abolishes the interaction of IgG4 with both FcγR and C1q, by disrupting the formation of a proline sandwich motif with the FcγRs, while leaving intact FcRn–IgG4 interactions and Fc stability.[136] Although FcRn polymorphism is known to affect IgG half-life,[137] no data are available specifically for anti-spike mAbs.

VIR-7832 (GSK, Brentford, UK) is a modification of sotrovimab with the addition of three amino acids (G236A/A330L/I332E, known as GAALIE) to the Fc domain, which enhance binding to FcγRIIa and FcγRIIIa, decrease affinity for FcγRIIb in vitro, and evoke protective $CD8^+$ T lymphocytes in vivo.[138,139] Although, to date, ablation of the Fc effector function has not been clinically used in mAbs against SARS-CoV-2, as we learn more about the pathogenesis of the virus and the mechanisms of antibody-mediated clearance, some of these alterations could find utility in future designs.

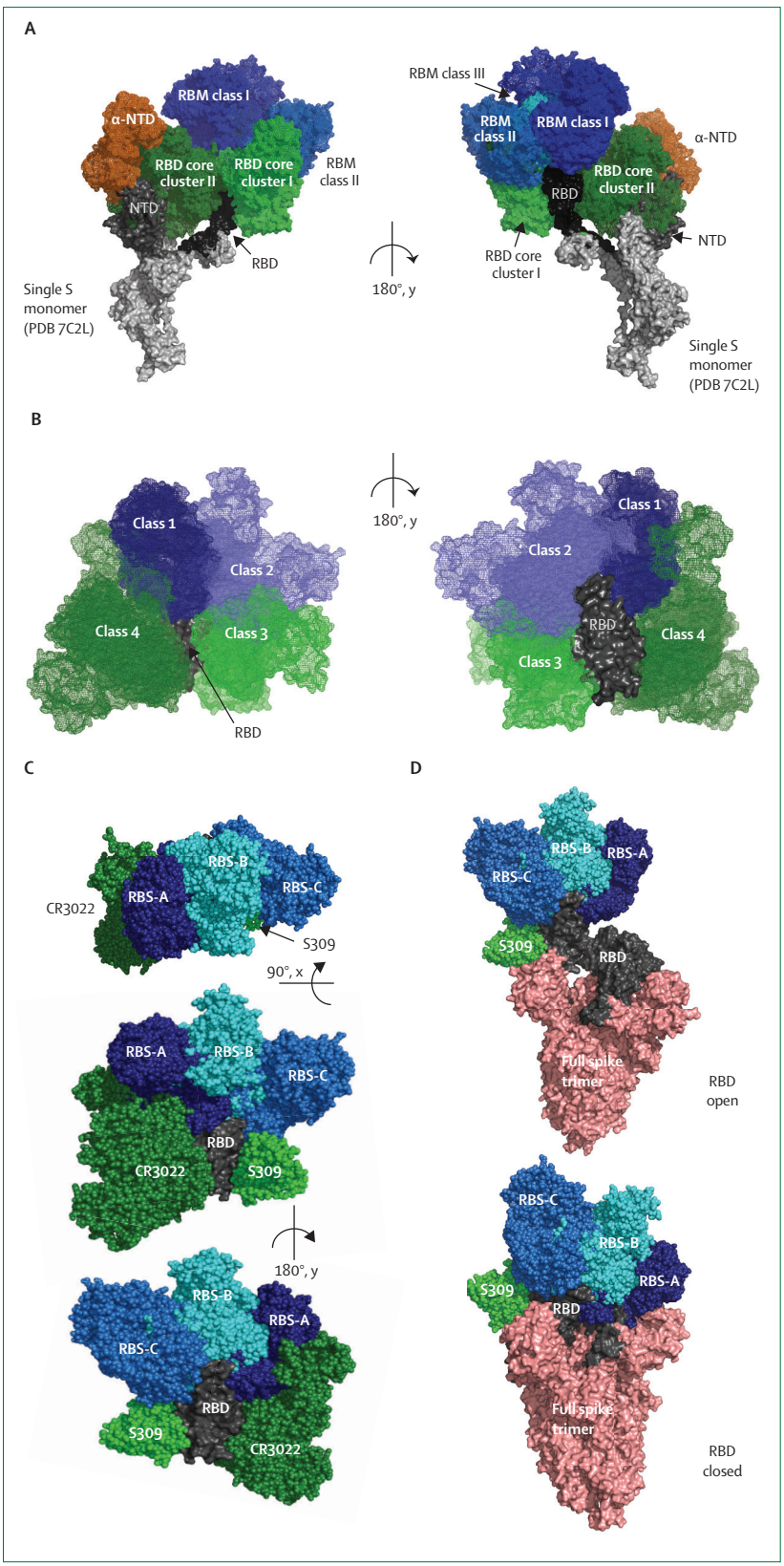
Expanding antigen specificity

Broadly neutralising antibodies targeting cross-reactive epitopes found in all or most variants are sought after when designing therapies for antigenically variable viruses, such as HIV-1 and SARS-CoV-2.[140] Within the genus Betacoronavirus, broadly neutralising antibodies have neutralising activity across all sarbecoviruses (appendix p 7).[141] Pan-sarbecovirus antibodies are elicited by BNT162b2 vaccination in SARS-CoV survivors.[142] Candidate pan-sarbecovirus mAbs targeting the spike protein have been variously referred to as cluster VII, class IV, or receptor binding domain (RBD) core cluster II (table 3, figure): examples of these mAbs include S2X259[40] and DH1047.[143] Other pan-sarbecovirus mAbs belong to the class I cluster I receptor-binding motif (RBM; eg, S2K146[31]) or class 3 (eg, sotrovimab), or bind to the base of the stem-helix at the HR2 boundary in the S2 subunit (eg, CV3-25,[144] 1249A8,[44] and the CC series[145]). Each of the S2 broadly neutralising antibodies have lower half-maximal inhibitory concentrations than anti-RBD antibodies, which could make the translation into clinically useful doses difficult; however, experiments in animal models suggest protection at low doses,[42,43] probably due to additional effector functions. Notably, each of these pan-sarbecovirus mAbs retains activity against omicron.[146]

	Variants of concern					Variants of interest							
	Alpha (B.1.1.7)	Beta (B.1.351)	Gamma (P.1)	Delta (B.1.617.2)	Omicron (B.1.1.529)	Zeta (P.2)	Epsilon (B.1.427 and B.1.429)	Theta (P.3)	Eta (B.1.525)	Iota (B.1.526 with E484K or S477N)	Kappa (B.1.617.1)	Mu (B.1.621)	Lambda (C.37)
Etesevimab	>5 FR[66,75]	No reduction[66]	>5 FR[75,76]	NA	>5 FR[77-90]	NA	3–5 FR[91]	NA	NA	No reduction[92]	NA	NA	NA
Bamlanivimab	>5 FR[66,93-95]	No reduction[66,95]	>5 FR[76,93,94]	>5 FR[96-101]	>5 FR[77-90,102]	>5 FR[95]	>5 FR[65,91]	NA	NA	>5 FR[92,103]	NA	NA	>5 FR[101]
Bebtelovimab	No reduction[67]	No reduction[67]	No reduction[67]	NA	No reduction against BA.1, BA.1.1, and BA.2[77,90]	NA	No reduction[67]	NA	NA	No reduction[67]	NA	NA	NA
Imdevimab	No reduction[66]	No reduction[66,104,105]	No reduction[75,76]	No reduction[105]	>5 FR[77-90,102,106-108]	NA	No reduction[91]	NA	NA	No reduction[92,103]	1–3 FR[109]	NA	1–3 FR[105,110]
Casirivimab	>5 FR[75]	>5 FR[66,104,105]	>5 FR[75,76,93]	>5 FR[105,109]	>5 FR[77-90,102,106-108]	NA	No reduction[91]	NA	NA	>5 FR[92,103]	1–3 FR[109]	NA	No reduction[105,110]
Regdanvimab	3–5 FR[111]	NA	>5 FR[112]	>5 FR[71]	>5 FR[82,84,87]	NA	3–5 FR;[91] >5 FR[71]	NA	NA	NA	>5 FR[71]	NA	NA
Tixagevimab	>5 FR[66]	>5 FR[66]	No reduction[76]	NA	>5 FR[77-79,82-84,87,89,90,102]	NA	NA	NA	NA	NA	NA	NA	NA
Cilgavimab	No reduction[66]	No reduction[66]	No reduction[76]	NA	>5 FR against BA.1 and BA.1.1;[77-79,82-84,87,102] 1–3 FR against BA.2[77,78,89,90]	NA	NA	NA	NA	NA	NA	NA	NA
C135 and C135-LS	No reduction[66]	No reduction[66]	NA	No reduction[113]	NA	NA	NA	NA	NA	NA	NA	NA	NA
C144 and C144-LS	NA	NA	NA	No reduction[113]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sotrovimab and VIR-7832	No reduction[66,73]	No reduction[66,73]	No reduction[73,76]	NA	1–3 FR against BA.1;[79-85,87,108] >5 FR against BA.2[77,78,89,90,106]	NA	NA	NA	NA	NA	NA	NA	NA
BGB-DXP604	NA	NA	NA	NA	1–3 FR[79]	NA	NA	NA	NA	NA	NA	NA	NA
BGB-DXP593	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Amubarvimab	NA	NA	NA	NA	>5 FR [77,79,83]	NA	NA	NA	NA	NA	NA	NA	NA
Romlusevimab	NA	NA	NA	NA	1–3 FR against BA.1;[77,83] >5 FR against BA.1.1 and BA.2[77]	NA	NA	NA	NA	NA	NA	NA	NA
Adintrevimab	No reduction[39]	No reduction[39]	No reduction[39]	No reduction[39]	>5 FR[39,77,82]	NA	NA	NA	NA	NA	NA	NA	NA

FR in geometric mean titre of neutralising antibodies for mAbs compared with the wild-type D614G SARS-CoV-2 strain (eg, Wuhan-Hu-1, USA-WA1/2020, B.1, or other reference strains). FR=fold reduction. mAbs=monoclonal antibodies. NA=data not available.

Table 4: **In-vitro efficacy of mAbs against SARS-CoV-2 variants of concern and variants of interest**



(Figure continues on next page)

Cocktails and bispecific antibodies

The experience with SARS-CoV-2 has shown that use of single mAbs is susceptible to losing their neutralising activity as new variants emerge, because of viral evolution or antibody selection of immune-escape mutants. Because of the large development costs associated with any antibody therapy, losing an existing therapy as a consequence of viral changes is a substantial loss with regard to clinical therapeutic options and monetary investment. Consequently, there is great interest in identifying epitopes that cannot be altered easily or generating mAb cocktails that reduce the likelihood of viral immune escape, by targeting the virus at more than one epitope (overlapping or not). In essence, combining mAbs creates a polyclonal product. Cocktails have been used against SARS-CoV-2 (table 1), Ebola virus, and rabies (CL184—a cocktail of two mAbs, CR57 and CR4098; Johnson & Johnson, New Brunswick, NJ, USA). Apart from protecting the product against viral evolution, cocktails also have the potential for triggering additive or synergistic effects through the action of two or more mAbs; however, cocktails with two or more mAbs are associated with substantially increased costs. Another alternative would be to create bispecific antibodies (eg, 14-H-06[147]), by combining two fragment antigen-binding regions that bind to different epitopes. Bispecific antibodies might be a cost-effective alternative to mAb cocktails and are a promising strategy to improve antibody potency and breadth.

Routes of administration

Immunoglobulins are large protein molecules, and only systemic routes have been investigated so far in clinical use. The initial approach of mAb therapy for COVID-19 used intravenous infusion, which was suitable for treating patients in hospital. After data suggested that mAb use in patients who were SARS-CoV-2 seropositive and being treated in hospital had no or marginal benefit, most subsequent clinical developments focused on individuals who were SARS-CoV-2 seronegative, involving primarily outpatients. The need to provide mAbs systemically to outpatients generally proved difficult since their administration required the existence of infusion facilities suitable for treating patients who were infectious. This issue led to alternative dosing routes of mAbs, such as subcutaneous (REGN-COV2) or intramuscular (AZD7442, sotrovimab, and adintrevimab) administration, which have been eventually authorised by different regulatory authorities since February, 2021.

The need for systemic administration is a problem for a therapy targeting a virus that replicates in the nasal epithelium, because only a proportion of serum IgG penetrates mucosal surfaces. Pharmacokinetic modelling suggests that, because of poor affinity to the polymeric Ig receptor, only one of 1000 IgG molecules infused intravenously reaches the respiratory mucosae.[148–150] Consequently, the most effective route of mAb delivery against a respiratory pathogen would be one that delivered

the mAb directly to the mucosa, such as intranasal or intratracheal administration. In parallel with mucosal vaccines,[151] passive immunotherapies are also being developed by taking advantage of mucosal immunity. Previous research suggested that fully human mAbs aggregated and lost activity after jet and ultrasonic nebulisation,[152–156] but did not when delivered with vibrating mesh nebulisers.[157–160] In particular, IN-006 is a muco-trapping formulation of regdanvimab that, when delivered via vibrating mesh nebuliser instead of being dosed intravenously, has resulted in 100 times higher mAb concentration levels in the lungs of rats than in serum.[161] Several investigators have proposed edible[162] or intranasal[163] egg-derived IgY for passive immunotherapy, and expression of viral antigens in the leaves of edible plants (eg, lettuce) is also being investigated to induce immunity.[164] Similarly, an inhalable, bispecific, single-domain antibody has been shown to neutralise omicron in a mouse model.[165]

Conclusions

The rapid deployment of multiple mAb therapies during the pandemic has been a remarkable human accomplishment. mAb therapies have undoubtedly saved thousands of lives by preventing progression of early disease to life-threatening conditions that would have otherwise required treatment in hospital. However, the experience of the past 2 years has also shown limitations of this approach, which could have been foreseen from what was known about antibody action and the antigenic variability of SARS-CoV-2. Although a few regulatory authorities promptly issued recommendations to avoid the inappropriate use of mAbs against resistant variants of concern as soon as they became locally dominant

E

Our proposed binning	Colour scheme in figure	Finkelstein et al (2021)[20] classification	Barnes et al (2020)[21] classification	Yuan et al (2021)[22] classification
1		NTD binding (strain-specific; antibody binding either prevents critical spike conformational changes or interferes with ACE2-binding site)	Not classified	Not classified
2		RBM class I (epitope directly overlaps with ACE2-binding site; RBD required to be in the up conformation. All members are strain-specific, and many have IGHV3-53 or IGHV3-66 heavy chain gene usage with a variety of light chains)	Class 1 (antibodies block ACE2; accessibility of RBD epitope only in up conformation)	RBS-A (some RBS-B; RBS-A epitope overlaps extensively with the ACE2-binding site)
3		RBM class II (strain-specific; epitope directly overlaps with ACE2-binding site, but less so than RBM class I members; therefore, they can bind RBD that is in up or down conformation)	Class 2 (antibodies block ACE2; accessibility of RBD epitope in up or down conformations)	RBS-C (antibodies target the back side of RBS on opposite site of RBS ridge, different angle of approach compared with RBS-A or RBS-B antibodies)
4		RBM class III (strain-specific; similar properties to RBM class II, except these antibodies make contact with nearby RBDs in addition to the ones they are bound to. This additional contact limits conformational motions and some antibodies even lock the trimer in a closed state)	Class 2	RBS-B (antibody straddles the RBS ridge where RBD Phe486 inserts into a pocket; located between the light and heavy chains of mAbs on the paratope surface; binds with more varied angles of approach than the RBS-A antibodies)
5		RBM core cluster I (antibodies prevent ACE2 from binding by either clashing with ACE2 or locking the spike homotrimer in a closed conformation. S309 can cross-neutralise SARS-CoV and SARS-CoV-2)	Class 3 (epitopes do not overlap with ACE2-binding site; accessibility of RBD epitope in up or down conformations)	S309 (antibody targets N343 glycan site, which corresponds to N330 of SARS-CoV; unique binding mode facilitated by hydrogen-bonding of core fucose moiety of N343 with mAbs of this class; less conserved than CR3022 site, but accessible in RBD up or down conformations; does not compete with ACE2-binding site, but can still be weakly neutralising)
6		RBM core cluster II (antibodies bind a cryptic epitope that is accessible only when the RBD is in the up conformation and, in some cases, open as well. These members are capable of disrupting the spike homotrimer and promoting S1 shedding. CR3022, EY6A, S304, H014, and VHH-72 can cross-neutralise SARS-CoV and SARS-CoV-2)	Class 4 (epitopes do not overlap with ACE2-binding site; accessibility of RBD epitope only in up conformation)	CR3022 (a SARS-CoV neutralising antibody, which binds conserved cryptic site on RBD and is non-neutralising for SARS-CoV-2; other antibodies in this class can also be neutralising [eg, COVA1-16, H014, EY6A, and ADI-56046]; CR3022 is the most frequent site targeted by cross-neutralising antibodies)

Figure: **Three-dimensional representation of spike epitopes targeted by mAbs approved to date according to different classifications**
For each spike glycoprotein epitope classification scheme, structural coordinates of anti-spike mAbs in complex with spike were collected and binned into classes described in each reference. Composite complexes were generated by aligning corresponding RBD monomers in each respective complex. Members of each class are listed in table 3. (A) Structures of anti-spike mAb classes adapted from Finkelstein and colleagues[20] are overlaid in complex with a single spike monomer (PDB 7C2L), with NTD and RBD domains. NTD binding, RBD core clusters I and II, and RBM classes I–III are displayed as mesh space-filling representation. (B) Structures of anti-spike mAb classes adapted from Barnes and colleagues[21] are overlaid in complex with a single RBD domain (PDB 7K8M). Antibody binding classes 1–4 are displayed as mesh space-filling. (C) Structures of anti-spike mAb classes adapted from Yuan and colleagues[22] are overlaid in complex with a single RBD domain (PDB 6XEY). Antibody binding classes RBS-A, RBS-B, RBS-C, CR3022, and S309 are displayed in spheres representation. (D) Classes RBS-A, RBS-B, and RBS-C adapted from Yuan and colleagues[22] are displayed in complex with the full spike trimer in the RBD open configuration (top, PDB 6VYB) and RBD closed configuration (bottom, PDB 6VXX) to show the accessibility of each epitope with respect to spike protein configuration. (E) Summary of anti-spike mAb classes, as described by Finkelstein and colleagues,[20] Barnes and colleagues,[21] and Yuan and colleagues.[22] Each classification was binned into six unifying categories for the purposes of this Review, on the basis of the descriptions and structural alignment of members of each class with available mAb-spike complex coordinates. mAb=monoclonal antibody. NTD=N-terminal domain. RBD=receptor-binding domain. RBM=receptor-binding motif. RBS=receptor-binding site.

Search strategy and selection criteria

We searched PubMed, medRxiv, and bioRxiv for articles published in English from Dec 1, 2019, to June 10, 2022, using the terms "anti-spike monoclonal antibodies" and the specific names of the monoclonal antibodies. We reviewed both the articles resulting from these searches and their references, and selected those articles relevant to the scope of this Review.

(NCT04501978),[115] the use of ineffective and costly treatments has often continued for months, thus wasting economical resources and increasing the incidence of unnecessary side-effects.[166] Such unjustified use of therapeutics is unacceptable in modern, evidence-based medicine, and can have serious consequences during a pandemic.

The clinical efficacy of mAbs has remained limited to patients with early and mild disease stages, as would be expected for a therapy that works primarily as an antiviral agent. Their high cost means that they are unlikely to become prominent treatment options in low-income and middle-income countries that cannot afford them. Scaling up of manufacturing is also a bottleneck for high-income economies, which often have had difficulties at procurement. Several lessons were learnt from the pandemic, such as the need for combining different (ideally non-overlapping) mAbs to minimise immune escape. Recombinant technology has been deployed to increase half-life and minimise off-target toxicity.

Overall, mAbs remain an important achievement of modern science, but their feasibility and economical sustainability against pathogens are likely to be maximal in small outbreaks and localised epidemics, rather than under pandemic settings. During a pandemic, an enormous number of affordable doses would be needed to have a positive impact on a global scale. In such instance, alternatives that are more robust and scalable than mAbs are preferred, such as convalescent plasma, or oral or intravenous small-chemical antivirals;[167] however, small-chemical antivirals are expensive and often associated with pharmacokinetic contraindications.

Contributors

DF wrote the first draft of the manuscript and designed the figure in the appendix. DF, EC, and GV designed the tables. SM designed the figure. MT and AC revised the manuscript.

Declaration of interests

AC is the Chair of the US National COVID-19 Convalescent Plasma Project and reports being part of the scientific advisory board of SAB Therapeutics, a company developing cow polyclonal antibodies. All other authors declare no competing interests.

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