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Review Article

Neutralizing monoclonal antibodies for COVID-19 treatment and prevention

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ABSTRACT

The SARS-CoV-2 pandemic has caused unprecedented global health and economic crises. Several vaccine approaches and repurposed drugs are currently under evaluation for safety and efficacy. However, none of them have been approved for COVID-19 yet. Meanwhile, several nMAbs targeting SARS-CoV-2 spike glycoprotein are in different stages of development and clinical testing. Preclinical studies have shown that cocktails of potent nMAbs targeting the receptor binding site of SARS-CoV-2, as well as broad-nMAbs targeting conserved regions within the virus spike, might be effective for the treatment and prophylaxis of COVID-19. Currently, several clinical trials have started to test safety, tolerability, PKs and efficacy of these nMAbs. One paramount limitation for the use of nMAbs in clinical settings is the production of large amounts of MAbs and the high costs related to it. Cooperation among public and private institutions coupled with speed of development, rapid safety evaluation and efficacy, and early planning for scale-up and manufacture will be critical for the control of COVID-19 pandemic.

In the last two decades, three different coronaviruses (CoVs) caused zoonotic outbreaks in humans: severe acute respiratory syndrome CoV (SARS-CoV, from now referred as SARS1) [1], Middle East respiratory syndrome CoV (MERS) [2] and more recently, severe acute respiratory syndrome CoV-2 (SARS-CoV-2, from now referred as SARS2) [3–6]. Compared to endemic human CoVs these three novel CoVs cause more severe acute respiratory disease and are associated with high fatality rates (9.6%, 34.4% and 0.6–3%, respectively) [7,8].

Although SARS2 has lower fatality rates compared to SARS1 and MERS, it spread much faster [9–11]. For that reason, the absolute number of deaths up to August 2020 is higher for SARS2 (776,157) compared to SARS1 (794) and MERS (858) [12]. Among patients infected with SARS2, the progression of disease is highly variable. Roughly, eighty percent of people that become infected with SARS2 develop mild or no symptoms; whereas the remaining 20% develop moderate to severe disease (termed COVID-19) [7,13–15]. COVID-19 severity

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has been associated with patient age, sex and comorbidities, being elder males with hypertension, diabetes and obesity among those with higher risk to develop respiratory failure and die. SARS2 pathogenicity, results from an acute excessive virus replication followed by an uncontrolled inflammation and an exacerbated immunity, explaining why in some patients, disease severity increases when viral load decreases [16,17].

SARS2 is a large enveloped RNA virus, containing a single-stranded, positive-sense RNA genome that encodes for a series of structural and non-structural proteins, as well as a group of accessory genes. The envelope spike (S) protein of CoVs is a trimeric type-1 integral membrane protein and class-1 fusion protein which possess 3 copies of an N-terminal subunit (S1) that mediates receptor attachment and 3 copies of a C-terminal subunit (S2) that mediates virus-cell membrane fusion. The S1 subunit contains 4 domains (A-D), being A (N-terminal) and B (receptor binding domain or RBD) the most relevant from an immunological point of view. The RBD of the spike glycoprotein (S) is poorly conserved among CoVs and, as a result, host receptor usage varies among different CoVs. Although SARS2 is closer to bat-SL-CoVZC45 and bat-SL-CoVZXC21 at the whole-genome level, the RBD of SARS2 is closer to that of SARS1 [18]. Interestingly, the RBD of SARS1 and SARS2 are 74% identical and both viruses use angiotensin-converting enzyme 2 (ACE2) present in the surface of target cells as receptor for docking and entry [3,18–21]. SARS1 and SARS2 RBD is subdivided in an N-terminal subdomain (RBD-NTD) and the receptor binding site (RBS). The homology of RBD-NTD and RBS between these two viruses is 83% and 50%, respectively. Post-attachment events are dependent on cellular proteases, such as transmembrane protease serine 2 (TMPRSS2) which cleave the spike protein and initiate a variety of conformational changes that are important for membrane fusion and entry.

SARS2 spike glycoprotein is the main target of neutralizing antibodies (NAbs) and several neutralizing monoclonal antibodies (nMAbs) targeting different epitopes within the virus spike have been recently described. Moreover, several preclinical studies have demonstrated that SARS2 nMAbs can suppress virus replication and disease severity in different animal models. In the absence of an effective treatment for COVID-19, passive immunization with nMAbs has recently gained interest as a therapeutic approach to reduce SARS2 impact in public health worldwide. In this article, I discuss advantages and challenges related to the use of nMAbs for treatment and prevention of COVID-19. References for this article were identified through searches of PubMed with search terms “SARS-CoV-2”, “COVID-19”, “neutralizing antibodies”, “monoclonal antibodies”, “therapy”, “prophylaxis” from December 2019 to August 2020. Additionally, the terms “SARS-CoV-2”, “COVID-19” and “monoclonal antibodies”, were searched at [ClinicalTrials.gov](https://www.clinicaltrials.gov). The final references were selected on the basis of relevance to the particular scope of this Review.

Antibody response in COVID-19 patients

In COVID-19 patients, viral load peak occurs concomitantly or shortly after symptoms onset. After peaking, viral load

decreases slowly and is detectable for up to 4 weeks [22,23]. However, infective virus has been isolated from the upper respiratory tract only within the first week after symptom onset [22]. As the virus replicates, the adaptive immunity is stimulated to generate cellular responses and antibodies (Abs), including NAbs in the majority of SARS2 infected symptomatic individuals [24]. IgM, IgG and IgA antibodies directed to SARS2 external S and internal N proteins develop within the first week after symptoms onset and peak two weeks after symptoms onset [22,23]. In 50% of individuals, seroconversion occurs one week after symptoms onset and 100% of individuals seroconvert by the end of the second week after symptom development [22,25–28]. Several studies reported an inverse correlation between viral loads and SARS2 specific-Abs; however, by the time that Abs develop, viral loads have already started to decrease indicating that innate and/or cellular adaptive immunity contribute to the initial virus containment [22,23,25]. Additionally, the Ab response can be weak or absent in asymptomatic or mild infections, suggesting at least a partial control of the virus by innate or T-cell mediated immunity [29,30]. Paradoxically, several studies have found a positive correlation between specific-Ab titers and disease severity, suggesting that a robust Ab response alone is insufficient to avoid severe disease and point out that the timing of Ab development might be crucial for efficient virus control [25,27,28,31,32]. The one-week gap between peak viral load and seroconversion suggests that the Ab response fails to efficiently control virus load during the first two weeks of infection and consequently, the excessive virus replication within this period could ignite the inflammatory process associated with severe disease. In addition, a larger antigenic exposure associated with virus replication might provoke the development of higher titers of antibodies in severe disease outcomes. Alternatively, it has been proposed that antibody dependent enhancement (ADE), a mechanism triggered by specific Abs, could potentially increase disease severity. ADE has been described for other viruses such as dengue virus (DENV) and respiratory syncytial virus (RSV) [33–35]. Although, ADE has also been described for SARS1 in vitro and in animal models, there is no evidence that this might happen in SARS2 infection in humans [36].

Oppositely, observations from several studies underscore a key antiviral effect of Abs, suggesting they might be a key immune correlate for protection against SARS2 infection: (i) seroconversion occurs in most COVID-19 patients [22,23,25] (ii) viral loads in SARS2 infected patients decrease after anti-S IgM and IgG antibodies development [22,23,25] (iii) memory B cells specific for SARS2 S antigens have been isolated and characterized from COVID-19 patients [30,37,38] (iv) NAbs induced in macaques after vaccination protect animals from development of disease after challenge with SARS2 [39] (v) macaques challenged with SARS2 develop a robust NAb response that protects them from reinfection after a second challenge [40,41] (vi) passive transfer of anti-SARS2 monoclonal NAb protects animals from disease after challenge with SARS2 [38,42,43]. Furthermore, a meta-analysis from 32 studies of SARS1 and severe influenza virus infection performed by Mair-Jenkins and colleagues showed a significant reduction in mortality following convalescent plasma (CP) therapy [44]. Additionally, two separate studies showed that CP therapy

administered to 15 severe/critically ill COVID-19 patients was followed by improvement in the patient clinical status. Interestingly, plasma treated patients had large reduction in viral loads and most were virus negative 3 days after infusion [45,46].

CoVs S protein and its RBD are highly immunogenic and most infected patients develop both anti-S and anti-RBD antibodies. Earlier during the pandemic, Hoffmann and colleagues showed that polyclonal Abs present in plasma from SARS1 infected individual could cross-react with SARS2 [21]. In a similar fashion, the plasma from COVID-19 convalescent patients cross-react with SARS1, and to a lesser extent with MERS and common cold CoVs [47]. Although the reactivity of COVID-19 plasmas against endemic CoVs has been associated with previous encounter to such type of viruses, its reactivity against MERS and SARS1 has proven to be due to cross-reactivity against conserved epitopes within S protein [47]. COVID-19 patients develop anti-S1 and anti-RBD antibodies; however, antibodies that effectively disrupt the binding of S protein and ACE2 receptor account for a small fraction of them [30,37,38,42,43,48,49].

Development of nMAbs for COVID-19

Anti-SARS2 nMAb discovery

Several monoclonal antibodies (MAbs) targeting the RBS of SARS1 have been described (i.e., CR3014, M396 and S230). Although these MAbs effectively neutralize SARS1 most of them do not cross neutralize SARS2, due to differences in the primary amino acid sequence of RBS among these viruses. However, these observations supported the discovery and characterization of SARS2 MAbs from COVID-19 patients. Over the past two decades, different programs from several institutions (i.e., NIAID Center for HIV/AIDS Vaccine Immunology, Vaccine Research Center, Pandemic Prevention Program (P3) program, etc.) have worked to define the platforms and enable technology for HIV vaccine development and rapid response to viral pandemics. From those, as well as other international initiatives, have come teams and technologies that are now responding to the COVID-19 epidemic to isolate SARS2 nMAbs [50]. As a result, several highly potent nMAbs targeting SARS2 RBD and S protein have been isolated using different approaches (i.e., immortalized EBV memory B cells, Ab isolation from mouse hybridomas, phage display libraries produced from llama immunized with prefusion-stabilized CoV spikes, direct cloning of Ig-encoding genes from isolated B cells sorted with fluorescent baits such as RBD and S-protein, microculture and supernatant screening of sorted memory B cells and single B cell NGS from sorted memory B cells, etc.) [30,37,38,42,43,47-49,51-61]. A description of these Abs can be found in Table 1. As observed for SARS1, highly potent nMAbs isolated from COVID-19 convalescent patients targeted the RBS and competed directly with ACE2 receptor binding. As expected, most of these nMAbs did not cross react with SARS1. In this regard, Ju and colleagues reported that despite partial homology between SARS1 and SARS2 RBDs, these domains might be immunologically different,

indicating cross reactivity could occur within S protein but outside ACE2-binding site [37].

Avoiding the emergence of virus resistance

Importantly, as observed earlier for SARS1, escape mutations were rapidly selected when single SARS2 MAbs were tested in vitro [62]. Furthermore, a natural mutation of SARS2 has now been detected at residue 495 (Y/N), which forms part of the ACE2 binding epitope. As RNA viruses are known to accumulate mutations over time, a big concern for any antiviral treatment is the risk for selection of treatment-induced escape viral-variants. In this regard, the discovery of novel nMAbs targeting different sites on SARS2 S protein will be extremely important to counteract the mutational capacity of the virus and avoid the emergence of resistant viral variants due to the administration of single drug therapy.

One strategy to prevent viral escape would be the use of antibodies targeting highly conserved epitopes on S protein. Toward this goal, Yuan and colleagues described a cryptic epitope located within the RBD but outside the RBS, which is conserved between SARS1 and SARS2 and is targeted by MAb CR3022 [63]. Interestingly, MAb CR3022, which has been isolated from a SARS1 infected patient [52] cross-neutralizes SARS2 by a mechanism that does not imply competition with ACE2 [53]. Different groups have isolated antibodies targeting the RBD-NTD with high neutralizing activity against SARS2. MAb S309, was isolated from immortalized B cell from a SARS1 infected patient [55]. This nMAb recognizes a glycan-containing epitope that is conserved within different SARS-related CoVs (sarbecovirus). In the second place, Wang and colleagues isolated 47D11 MAb from SARS1 mouse hybridoma [54]. As it is the case with CR3022, none of these MAbs compete with receptor attachment. More recently, Lv and colleagues described a novel humanized-nMAb, H014, that prevents attachment of SARS2 to its host cell receptors [64]. In this opportunity, the authors constructed an antibody library generated from RNAs extracted from peripheral lymphocytes of mice immunized with recombinant SARS1 RBD and then, they screened the phage antibody library using a SARS2-RBD. As described for S309 and 47D11, H014 binds to an epitope within the RBD, but different to RBS, which allows these antibodies to cross-neutralize both SARS1 and SARS2. However, in the case of H014, the interaction between the antibody and S protein interferes with receptor binding. In a separate study, Wec and colleagues screened memory B cells from a SARS1-survivor and found 8 SARS2 cross-reactive MAbs targeting a single continuous patch in the surface of the RBD [56]. This highly conserved area which spans from ACE2-binding site to the epitope recognized by MAb CR3022 explains cross-reactivity found in these set of antibodies. In addition, Wrapp and colleagues isolated SARS-VHH-72, a single chain antibody from a llama immunized with prefusion-stabilized SARS1 spike that cross reacted with SARS2 [57]. SARS VHH-72 prevents the binding of ACE2 through a partially overlapping epitope of MAb CR3022. When two copies of this VHH were coupled as a bi-valent IgG-Fc fusion (named VHH72-Fc) the construct was also able to neutralize SARS2. Considering that

Table 1 SARS-CoV-2 mAbs.

Specificity	Name	Source	Isolation method	Potency (IC ₅₀)	Preclinical trial	Clinical trial
SARS2-RBD. Competes w/ ACE2 binding and promotes S1 dissociation	REGN-10987 [60,62,66] (REGN-10933) ^a	SARS2-S/RBD immunized hu-mice and COVID19 patient	single MBC sorting (RBD bait) followed by single cell antibody cloning	pV: <10 ng/ml	Rhesus macaques and golden hamsters	NCT04426695 (I-III) NCT04425629 (I-III) NCT04452318 (I-III)
	P2C-1F11 [37] (P2C-1C10, P2B-2FG) ^a	COVID19 patient		pV: 30 ng/ml (P2C-1F11)	NA	NCT04479631 (I) NCT04479644 (I)
	CB6-LALA [43] (CA1)			V: 36 ng/mL	Rhesus macaques	NCT04441918 (I)
	C105 [47]			pV: 26 ng/ml	NA	NA
	C002 [30] (C121) ^a			V: 10 ng/ml	NA	NA
	nAB cc12.1 [38] (nAB c12.23)			V: 19 ng/ml (cc12.1)	Syrian hamsters	NA
	B38 [42] (H4) ^a			V: 200 ng/ml	hACE2-transgenic mice	NA
	311mAb-31B5 [48] (32D4)			pV: 50 ng/ml	NA	NA
	COVA1-18 [61] (COVA2-15, COVA2-17) ^a	COVID19 patient	single MBC sorting (stabilized pre-fusion SARS2-S bait) followed by single cell antibody cloning	RBD mAbs pV: 7 ng/ml	NA	NA
	CV30 [58] (CV1) ^a			pV: 30 ng/ml (CV30) and 15000 ng/ml (CV1)	NA	NA
COV2-2196 [59] (COV2-2130)	COVID19 patient	single MBC sorting (SARS2-S bait) followed by single cell antibody cloning	V: 1–10 ng/ml	hACE2-expressing mice (AdV-hACE2 transduction)	NA	
BD-368-2 [49]		single-cell RNA (VD)) sequencing of antigen (RBD & S)-enriched B cells	V: 15 ng/mL	hACE2-transgenic mice	NA	
SARS2-S NTD, without competing ACE2 binding	4A8 [51]	COVID19 patient	single MBC plasmablasts sorting (SARS2 stabilized spike-derived ectodomain bait) followed by single cell antibody cloning	V: 500 ng/ml	NA	NA
Cross-neutralization SARS1/SARS2. RBD attachment without competing ACE2 binding	CR3022 [52,53,63]	SARS1 patient	SARS1-reactive mAb selected from a single-chain Fv phage display library reconstructed into IgG1 format	V: 114 ng/mL	NA	NA
	47D11-H2L2 [54]	SARS1 S hybridoma's derived from immunized transgenic H2L2 mice	supernatant screening for reactivity against SARS2-S1 by ELISA and SARS2 pV neutralization	V: 570 ng/ml	NA	NA
	S309 [55]	Immortalized memory B cells from SARS1 patient	supernatant screening for reactivity against SARS-CoV-2 S by ELISA	V: 79 ng/ml	NA	NA
Cross-neutralization SARS1/SARS2. RBD attachment competing with ACE2 binding and promoting S1 dissociation	H014 [64]	mice immunized with SARS1 RBD	phage display panning using SARS2 RBD	V: 38 ng/mL	hACE2-transgenic mice	NCT04483375 (I)
	ADI55689 [56] (ADI56046) ^a	PBMCs from SARS1 infected patient	single MBC sorting (RBD bait) followed by single cell antibody cloning	V: 50–1400 ng/ml	NA	NA
	VHH72-Fc [57]	llama immunized with prefusion-stabilized CoV S	phage display panning using SARS1 or MERS S proteins	Two VHH coupled as a bivalent IgG-Fc fusion needed for neutralization	NA	NA

Abbreviations: pV: pseudovirus assay was used to determine neutralization potency; V: authentic live virus was used to determine neutralization potency; (I), (II), (III): clinical trial phase; NA: not assayed.

^a 2 or more different epitopes.

this novel site of vulnerability located towards the RBD-NTD of S protein is not exposed in the pre-fusion state and that some residues are indispensable for granting spike stability, mutations at this point would be less frequent and if they occur, they might have a strong negative impact in viral fitness. For that reason, Abs targeting this particular site of neutralization might be more resistant to virus escape. Another site of vulnerability targeted by cross-reactive nMAbs consists in the N-terminal region of S1 protein [47,51,56]. Chi and colleagues described MAb 4A8 targeting this particular region on SARS2 S protein [51]. Finally, Liu and colleagues isolated potent and diverse nMAbs targeting several epitopes on SARS2 spike [65]. Apart from those antibodies directed to the RBD and NTD, the author described two nMAbs targeting novel quaternary epitopes located on top of SARS2 spike.

Expanding the number of potent nMAbs with different specificities against S protein will allow the formulation of more effective nMAB cocktails; such combination of nMAbs accounting for different specificities may provide a powerful way to minimize mutational escape by SARS2 [62]. Moreover, the rational development of nMAB cocktails targeting different sites of vulnerability within the S protein could confer a synergistic neutralizing effect. Anti-SARS2 nMAbs described in Table 1 have been characterized in detail by *in vitro* binding affinity, epitope mapping by competition assays, target specificity by cryo-EM and most importantly, for *in vitro* and *in vivo* neutralization, using different platforms. Remarkably, these antibodies have proven to be effective preventing infection of target cells, and most importantly blunting virus replication and pathogenicity in different animal models (i.e. hu-ACE2 transgenic mice, Syrian golden hamster and non-human primates (NHPs) [38,42,43,49,64,66]. Overall, these studies indicate that several nMAbs have the potential to be used either prophylactically or therapeutically to avoid and/or control SARS2 infection.

Effector mechanism triggered by nMAbs

IgG contains two antigen combining sites (Fabs) and an Fc region that interacts with various Fc receptors (FcRs) on immune cells. MAbs differ from antiviral drugs in that in addition to potent viral particle neutralization and high specificity they can engage the host immune cells (i.e., NK, neutrophils and macrophages) through their FcRs and trigger several immune effector mechanisms (i.e., antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and antibody-dependent cellular viral inhibition); furthermore, MAbs can induce complement-dependent cytotoxicity through their Fc domain [67]. Altogether, these effector functions triggered by MAbs contribute towards controlling viral replication. In addition, MAbs can bind viral antigens to form immune complexes (ICs) that enhance antigen presentation and boost endogenous immune responses in a mechanism known as “vaccine-like effect” [68]. Different studies have shown that besides potent neutralization, anti-SARS2 Abs effectively trigger FcR present in effector cells, providing additional protective mechanisms *in vitro* and *in vivo* [39,40,55,60]. These results suggest that Fc engineering could potentially enhance these antiviral effects as it has been

demonstrated for other viral diseases [69]. Even though Fc-FcR interactions can enhance immunity in a favorable way, they can also lead to disease enhancement. The risks of ADE will need to be further evaluated for SARS2. Meanwhile, in the context of human studies it would be possible to use engineered MAbs with reduced FcR binding to minimize potential ADE effects. In this regard, both complement and FcR binding could be abolished with a double mutation at the Fc region of the antibody (L234A/L235A) [70]. By introducing this LALA double mutation within the Fc region of anti-SARS2 CB6 MAB, Shi and colleagues showed in macaques that the antiviral efficacy of CB6-LALA was not affected [43].

From the bench to the bedside

SARS2 has already caused a great impact globally, and it is expected that subsequent waves of infection will hit regions that are currently recovering from devastating initial COVID-19 outbreaks. In the absence of a vaccine, a high proportion of human global population might become infected in the next years. Experts in this field have estimated that testing, large scale production and distribution of an effective vaccine might take from 1 to 2 years [71]. Considering that there is no effective treatment the number of deaths will also increase exponentially during the next years. Under the current situation, novel preventive approaches are in great need. Passive immunization with NAbs has recently gained interest as the most convenient approach to fulfill this gap and reduce SARS2 impact in public health worldwide [72–74]. The reduction of SARS2 viral load by NAbs, as observed in CP pilot trials suggest that SARS2 infection in humans can be modulated using passive immunization in clinical settings. Compared to CP, nMAbs can be thoroughly characterized *in vitro*. In addition, the ability to control dosing and cocktails composition improves the efficacy of nMAbs over CP. Furthermore, the use of MAbs with highly potent neutralizing activity can reduce the risks of ADE, compared to the polyclonal mixture of Abs present in the plasma. Recent studies with patients infected with Ebola highlight the higher efficacy of nMAbs over CP treatment [75]. The finding that ansuvimab (MAB114) is safe and effective reducing the mortality rate of Ebola virus disease from 67% to 34%, underscore the potential use of MAB therapy during a deadly infectious disease outbreak [75–77]. For HIV-1, another lethal pandemic virus, it took more than 30 years to discover effective nMAbs capable of neutralizing most circulating HIV-1 isolates [78–82]. Following a detailed molecular characterization and efficacy pre-clinical trials, only few of these antibodies have reached clinical settings [83–88]. Proof of concept phase 2 clinical trials showed a partial efficacy of single nMAB treatment in controlling viremia due to the selection of resistant viral mutants; currently, combination of HIV-1-nMAbs with different specificities are being tested in order to avoid the emergence of virus resistance. Compared to HIV-1, SARS2 accounts for a lower mutation rate. In addition, it has not been reported that CoVs produce persistent infection and no within-host viral reservoir has been described for SARS2 or other CoVs, as for HIV-1. Altogether, these observations and the fact that *in vitro* neutralizing activity of SARS2 nMAbs is higher than nMAbs against Ebola and HIV-1, suggest

that passive immunization with SARS2 nMAbs could be used to protect from COVID-19.

Pre-exposure administration of SARS2 nMAbs

In addition to the post-exposure treatment, nMAbs can also be used prophylactically. The first FDA-approved MAb against infectious diseases, Palivizumab, is indicated for prevention of respiratory syncytia virus (RSV) infection in preterm infants and children at high-risk for development of severe respiratory disease [89]. For HIV-1, two large scale phase 2b clinical trials –AMP trials, enrolling 4200 participants– have been initiated to test the efficacy of prototype MAb VRC01 in preventing HIV-1 acquisition in high risk populations (NCT02716675 and NCT02568215) [90]. Several points will have to be considered if SARS2 MAbs are intended to be used prophylactically in populations at high-risk of acquiring infection or developing severe COVID-19 disease. It has been shown in animal models for HIV-1 infection that if administered pre-exposure, MAb treatment can block infection and interfere with the development of the adaptive immunity [91–93]. If this is also true for SARS2, then successive MAb doses should be administered in order to avoid the acquisition of infection, until an effective and safe method capable of inducing long-term immunity becomes available (i.e. vaccine). As a consequence of repetitive parenteral administration of an exogenous drug, anti-drug immunity can frequently decrease treatment efficacy. Although the use of human or fully humanized MAbs reduce such type of anti-MAb response, the constant exposure of a single MAb paratope might induce the development of anti-drug immunity. However, such type of undesirable effect was not observed following repetitive (up to 11 doses) subcutaneous and intravenous administration of VRC01 in human volunteers as reported by Mayer and colleagues [94]. If detected in upcoming trials, such unwanted effect could be avoided by the sequential administration of nMAbs with different specificities.

Importantly, antibody half-life and biodistribution could significantly impact the efficacy of the therapy. While half-lives of most antiretroviral drugs range between a few hours to 2 days, the half-lives of nMAbs are measured in weeks and these periods can be further extended by modification of the antibody Fc domains that enhance the affinity to the neonatal Fc receptor (FcRn) [95]. The FcRn interacts with the Fc region of IgG and is involved in recycling of IgG within cells. This interaction is also involved in actively transporting IgGs to sites of pathogen encounter [96]. For example, the M428L and N434S (“LS”) mutations prolong antibody half-life without compromising antigen-binding or other Fc-mediated functions [97]. In the case of VRC01, the FcRn enhancing mutation VRC01-LS [95] lead to 2–3 fold higher in vivo half-life in macaques compared to VRC01. In addition, increased and prolonged levels of VRC01-LS were detected in vaginal and rectal mucosal tissue compared to the unmodified VRC01 [96,97]. Recently, Griffin and colleagues showed that a single intramuscular dose of Nirsevimab protected infants for an entire RSV season [98]. Nirsevimab is engineered with a triple-amino-acid (M252Y/S254T/T256E, “YTE”) substitution within its Fc region. The YTE mutation also enhances the binding of

the IgG to the FcRn prolonging the serum half-life of this antibody.

Another limitation to the use of nMAbs in clinical settings is due to the fact that intravenous route employed in most nMab clinical trials can be impractical. Subcutaneous (SC) injection, however, allows for self-administration, showing similar nMab half-lives and biodistribution [83,94]. Thus, SC administration of highly potent nMAbs targeting SARS2 S protein and accounting for an extended half-life, may facilitate dosing every few weeks to several months for prevention. Moreover, FcRn-mediated transport may increase the MAb levels in respiratory mucosa, where it might confer higher protection against SARS2 infection.

Adverse events associated with MAb administration

MAbs are currently established as targeted therapies for malignancies, transplant rejection, autoimmune and infectious diseases. Among the advantages of MAbs over conventional drugs are their high specificities, their long half-lives and their good risk–benefit ratio; moreover, regulatory approval rates for MAbs are about 20% compared with 5% for new chemical entities [99]. However, intravenous administration of MAbs carries the risk of immune reactions such as acute anaphylaxis, serum sickness and the generation of anti-drug antibodies. In addition, there are numerous adverse effects of MAbs that are related to their specific targets, including the development of infections and cancer, autoimmune disease, and organ-specific adverse events such as cardiotoxicity [100]. However, most of these adverse effects are related to the immunomodulatory effect of MAbs targeting different endogenous immune mediators (i.e., immune system checkpoints, cytokine and cytokine receptors, etc.) and are expected to be absent for MAbs targeting exogenous viral epitopes. As mentioned earlier, recent technical advances have allowed the transition from mouse, via chimeric and humanized, to fully human MAbs, with a reduction in potentially immunogenic mouse components. In addition, molecular engineering has enabled the fine-tuning of MAb function to enhance their effects and to minimize immunogenicity and side effects. Remarkably, no serious adverse events were reported in several phase 1 and 2 clinical trials administering up to 11-doses of anti-HIV-1 nMAbs [87,88,94,101].

The challenge of increasing scale production of MAbs

An important restriction of the use of MAbs in clinical settings is related to the manufacture of large amounts of MAbs, as well as the high costs associated with it. Currently, MAb production platforms are based on the cloning of Ig-encoding genes from isolated specific-B cells. This technique involves PCR amplification of Ig-encoding genes from B cells, cloning them into an expression vector and re-expression in different mammalian cells. Batch productions can be scaled from 20 to 200 L (initial phase 1–3 trials) to 12,500 L (commercial manufacturer), at an average yield of 1 g/L. For example, when Boehringer Ingelheim (Ingelheim, DE) handled the production of Palivizumab (previously done by MedImmune) they scaled up from 400 to 12,500 L reactors, allowing a total production of 70 kg/year (about 560,000 standard units (SU) 120 mg each).

Other example is Pembrolizumab, an anti-PD-1 MAb used for the treatment of several types of cancer; in 2019 Merck and Co. (MSD, NJ, US) produced about 200 Kg of Pembrolizumab. In the case of VRC01, used for the AMP trials, the Vaccine Research Center (VRC-NIAID, MD, US) manufactured a total of 60 Kg of MAb for administration in different treatment groups (10 mg/kg or 30 mg/kg; a total of 10 consecutive doses). Although the production of this amount of VRC01 took more than one year, the fact that the VRC is an institution dependent from de National Institute of Health (NIH, MD, US), points out that such large production scale can be achieved either by private or public sector. Most importantly, if effective, anti-SARS2 MAbs produced at those levels could save 100s thousands lives. Of note, the amount of antibody necessary for treating a specific viral infectious disease will depend on the regimen of administration and the dose needed to achieve the desired antiviral activity. Such dose will be influenced by the potency and the half-life of each particular MAb. The discovery of extremely potent nMAbs against SARS2, coupled to a bio-engineered upgrade (i.e., greater neutralization potency, breadth, extended half-life and proper biodistribution) will significantly reduce the number of doses and dosage needed, and most importantly, its cost.

Clinical testing of SARS2 nMAbs

Several private companies specialized in MAb discovery and development have engaged in partnerships with government and large-scale pharmaceutical companies in order to collaborate in the development, testing, cGMP clinical manufacturing and commercialization and global distribution of several SARS2 MAbs. From a total of 89 MAbs, 14 are being tested in phase 1–3 clinical trials, for safety, tolerability and pharmacokinetics (PKs) determination. In addition, some candidates are being tested for preliminary efficacy, with the option to extend the number of participants if preliminary data is satisfactory. Junshi Biosciences (Shanghai, CN), has started a phase 1 clinical trial (NCT04441918) for JS016 (MAb CB6, [Table 1]) in 40 healthy patients in China. CB6 targets SARS-2 RBS and specifically competes with ACE2 binding. Besides accounting for a high neutralization potency in vitro, CB6 effectively prevented and/or controlled SARS2 infection in non-human primate (NHP) model. The company also announced an agreement with Lilly and Co (IN, US) to start the large scale production of this Ab in the US. Regeneron Pharmaceuticals (NY, US) has also announced the beginning of a series of phase 1–3 combined clinical trials with REGN-COV2 a nMAb cocktail of two nMAbs (REGN-10987 and REGN-10933, [Table 1]). Both MAbs target different epitopes on SARS-2 RBS and compete with ACE2 binding. As reported in preclinical studies the combination of these two potentially neutralizing MAbs avoided the generation of resistant viral variants in vitro. The first of these studies (NCT04426695) will engage 1860 hospitalized adults with COVID-19 to study the REGN-COV2 safety, tolerability and efficacy following a single intravenous dose of the cocktail. The second study (NCT04425629), will test REGN-COV2 in 1054 ambulatory adult patients with COVID-19. A third study (NCT04452318) will assess the efficacy of REGN-COV2 preventing SARS2 infection in household contacts of individual infected with SARS2. If

preliminary results from these trials are favorable, Regeneron plans to produce 100s thousand doses of this cocktail by the end of 2020 and also expect to produce 10 Million doses during 2021. A similar approach is also being tested by AstraZeneca (London, UK) in collaboration with Vanderbilt University Medical Center (TN, US) (COV2-2196 and COV2-2130). Another common strategy to safeguard against viral escape to antibody therapeutics involves selection of antibodies binding to conserved epitopes. In this regard, Vir Biotechnology (CA, US), in association with Wu Xi Biologics (CN), Biogen (MA, US), GSK (Brentford, UK) and Samsung (Seoul, KR), are planning to start clinical trials using different SARS1/SARS2 cross-reactive nMAbs. nMAbs VIR7831 and VIR7832, target conserved epitopes on S protein of both CoVs; mutations in Fc have been incorporated to these MAbs to extend half-life and increase FcR engagement. The company is planning to test these MAbs individually, and if effective they expect to produce 10 Million doses in 2021. Abcellera Biologics (Vancouver, CA) developed LY-COV555 (LY3819253) in collaboration with VRC-NIAID. They have recently signed an agreement with Lilly and Co to scale up the production and commercialization of this SARS2-S protein nMAb which started phase 1 clinical trial engaging 40 COVID-19 hospitalized patients (NCT04411628). In parallel they are running a phase 2 clinical trial to test MAb efficacy in 400 early mild-to-moderate COVID-19 patients (NCT04427501). The company expect to scale up the production to 100s thousand doses by end 2020. More recently, Bria Biosciences LTD (Beijing, CN) launched a couple of phase 1 clinical trials, enrolling 12 participants each, to test the safety of two different antibodies administered separately: BRII196 (NCT04479631) and BRII198 (NCT04479644) [Table 1]. In addition, Sinocelltech LTD (Beijing, CN) is enrolling 33 participants into a phase 1 clinical trial for nMAb SCTA01/H014 (NCT04483375) [Table 1]. Furthermore, TYCHAN (SG) started a phase 1 clinical trial to test TY027 MAb (NCT04429529) in 25 healthy adults and Sorrento therapeutics is doing the same with STI-1499 MAb (NCT04454398), in 24 hospitalized COVID-19 patients. It is anticipated that several other anti-SARS2 nMAbs will resume clinical trials in the short future. Finally, Celltrion Healthcare (KR) announced they will start a phase 1 clinical trial to test nMAb CT-P59.

Conclusions

The SARS2 pandemic has caused unprecedented global health and economic damages, and the situation is not under control yet. National Health Services worldwide, including those from the most developed countries were overwhelmed due to a high amount of severe ill patients in a reduced time-frame, and thousands of lives were lost due to unpreparedness and controversial political decisions. Although several vaccine candidates and repurposed drugs are currently being evaluated for safety and efficacy in record time, none of them have been approved for COVID-19 use. Experts in the field agree that once effective vaccines become available, universal accessibility has to be granted. Additionally, some populations might not respond well to it (i.e., the elderly or immunocompromised).

Several nMAbs targeting different epitopes on SARS2 spike protein are being tested for the prevention and treatment of COVID-19. The combination of potent-nMAbs targeting the RBS and broad-nMAbs targeting conserved regions within the spike protein of SARS1 and SARS2 might increase treatment efficacy, by avoiding the emergence of resistant viral variants. Preclinical studies carried out in different animal models suggest that pre-exposure use of SARS2 nMAbs might prevent or at least reduce disease severity in people at high risk of acquiring infection (i.e., people at nursing facilities, confirmed case householders, health care workers, etc.). Additionally, SARS2 nMAbs could be administered early during COVID-19 infection in those patients at high risk of developing severe disease, for example the elderly and patients with pre-existing conditions. By modulating acute virus replication, an early nMAb intervention in this particular population could induce a better outcome of the disease. Currently, several clinical trials have started to test the safety, tolerability, PKs and efficacy of SARS2 nMAbs using either a prophylactic or therapeutic approach. These proof-of-concept trials will inform about the importance of NABs as a correlate of protection against SARS2 in human population. Observations from these trials will be fundamental for future clinical management of COVID-19, as well as for vaccine development. Besides the emergence of virus resistance, another paramount limitation for the use of nMAbs in clinical settings is associated with the manufacture of large amounts of MAbs and the high costs linked to it. Cooperation among public and private institutions coupled with speed of development, rapid safety and efficacy evaluation, and early planning for scale-up and manufacture will be critical for the control of COVID-19 pandemic.

Declaration of competing interest

The author does not have any competing interest to declare.

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