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Viewpoint

Engineering monoclonal antibodies for COVID-19 prophylaxis

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The therapeutic and prophylactic uses of monoclonal antibodies (mABs) against SARS-CoV-2 are limited by their short half-life and need for intravenous delivery. In this issue, Cobb et al.[1] engineer a neutralizing mAB cocktail with extended half-life that can be delivered intramuscularly to provide prophylactic protection against infection in rhesus macaques.

Monoclonal antibodies (mABs) are now under emergency use authorization to treat COVID-19, where the viral target is susceptible. However, mABs have limited half-life and durability and typically require intravenous delivery, diminishing their use as broadly deployable interventions.

Cobb et al. report that combination of two SARS-CoV-2 neutralizing mABs (ADM03820) targeting non-overlapping epitopes on spike receptor binding domain (RBD) is an effective prophylaxis against infection in cynomolgus macaques.[1] ADM03820 contains variant Fc regions that extend half-life (M252Y/S254T/T256E mutations, designated YTE) and limit effector functions, such as binding to Fcγ-receptor (L234A/L235A, designated LALA). *In vitro*, ADM03820 potently neutralizes Alpha, Beta, Delta, and Gamma variants of SARS-CoV-2.

After ADM03820 administration either intramuscularly or intravenously, antibodies were detectable in circulation, nasopharynx, and lung (bronchioalveolar-lavage [BAL]). When given 3 days before viral challenge, ADM03820 resulted in dose-dependent decreases in viral replication, detected by PCR of sgRNA, in nasopharynx and lung BAL. In animals given highest dose of ADM03820 IM or IV, all animals eliminated detectable virus by day 2 post-infection. Individually, ADM03820 provided dose-dependent protection in lung. High doses of individual mAB provided similar protection in nasopharynx; however, higher viral loads were detected in animals treated with lower antibody concentration, likely representing viral breakthrough. Lower dose ADM03820 offered higher protection in lung BAL compared to nasopharynx, where increased viral loads were seen across decreasing dose conditions. Differences in immunity between upper and lower airway are discussed elsewhere[2] and are important in defining breakthrough infection. Current SARS-CoV-2 vaccines elicit anti-spike IgG detectable peripherally. Immunity from vaccines or mABs in nasopharynx requires further study.[2] Lung and nasopharynx may have differential distribution of antibody transporters suitable for IgG or IgA may be necessary for protection in nasopharynx. While possible that ADM03820 turnover differs between nasopharynx and lung, ADM03820 was detectable at similar levels in BAL and nasopharyngeal-swabs up to 60 days. Sham-treated animals developed low-level neutralizing titers at day 6, attributed to natural immunity induction.[1] Future studies are warranted to study differences in immunity afforded by mABs, including ADM03820, in upper and lower airway. Finally, the authors define thresholds for mAB concentration associated with protection against SARS-CoV-2 challenges.

Combined noncompeting antibody cocktails against SARS-CoV-2 spike prevent mutational escape,[3] providing a rationale to develop antibody cocktails providing protection across variants. This study supports use of mABs as pre-exposure prophylaxis, in addition to conventional post-exposure treatment, provided the cocktail targets the prevailing circulating strain. This study supports IM administration of ADM03820, which is more broadly deployable than IV administration as a public health strategy.

Protective serum antibody neutralizing titer for ADM03820 is 6000 (NT_{50}).[1] Protective serum antibody neutralizing titer induced by vaccines in non-human-primates (NHPs)[4] and humans[5] is estimated to be less than 6000. This is significant because ADM03820 lacks Fc effector functions; therefore, protection is from direct humoral neutralization. Future investigations may elucidate why ADM03820 has a higher NT_{50} than vaccines and duration of neutralizing titer, which is important to support use of ADM03820 as prophylaxis. Since ADM03820 lacks Fc-mediated effector functions, there is possibly decreased complementary T cell immunity. ADM03820 only targets two epitopes compared to vaccine-induced humoral immunity, which may generate antibodies against a larger number of epitopes. Nevertheless, lack of Fc-mediator function in ADM03820 demonstrates that humoral immunity itself sufficiently eliminates

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virus in the cynomolgus macaque. This study demonstrates the value of NHP models for evaluating pharmacokinetics of mABs given IM and IV and estimating protection thresholds. While estimated protection thresholds need to be confirmed through additional studies, the estimation methods and analysis in a NHP model represent a significant advance in evaluating mABs.

Limited half-life of mABs is a major concern for prophylactic use against infection. By developing Fc region-modifications, Cobb et al. suggest an extended half-life for ADM03820. Cobb et al. propose that since another duo of antibodies (AZD7442) utilizing YTE Fc modifications last up to 12 months in humans,[6] ADM03820 may also last for 12 months. YTE increased affinity of AZD7442 for FcRN (neonatal Fc receptor), which rescues antibodies from lysosomal degradation and promotes recycling to cell surface, leading to increased half-life. AZD7442 contained "TM" modifications to reduce Fc receptor interactions, while ADM03820 contained "LALA" mutations to reduce Fc receptor interactions. Additional studies are warranted to confirm half-life of ADM03820 antibodies in NHPs and humans, determine efficacy of repeated administrations, and identify protection in non-respiratory organs. IM administration of ADM03820 is currently being tested in a phase 1 human clinical trial (NCT04592549).

It is unknown whether ADM03820 has protective effects beyond viral neutralization in the elderly or in comorbid states, since prophylactic antibody treatment may be an alternate for high-risk individuals who cannot be adequately vaccinated or whom may not elicit potent immune response. SARS-CoV-2 infection results in dysregulated immune and inflammatory response, which exacerbates tissue damage, and may lead to post-acute sequelae. Administration of two prophylactic mABs, C144-LS and C135-LS, targeting the spike RBD protect aged, diabetic rhesus macaques from SARS-CoV-2 viral replication as well as immune activation by significantly limiting interferon-induced chemokines and CD4 T cell influx into cerebrospinal fluid.[7] Prophylactic C144-LS and C135-LS given 75 days before infection in rhesus macaques protected from disease.[8] Administration of C144-LS and C135-LS after challenge provided respiratory protection.[8] C144-LS and C135-LS contained Met428Leu/Asn434Ser (LS) mutations that increased interaction with FcRn, explaining the duration of protection.[8] Studies investigating ADM03820, C144-LS and C135-LS, or AZD7442 provide evidence for Fc modifications to extend half-life in mABs for prevention or treatment of SARS-CoV-2 disease.

This timely study adds to the growing evidence for mABs as prophylaxis for those unable to be vaccinated or for whom vaccination may not elicit protective immune responses against SARS-CoV-2. It is critical to evaluate prophylactic and treatment efficacy of ADM03820 against emerging variants such as Omicron. Cobb et. al.[1] show that modifying antibody Fc regions can extend half-life and demonstrate efficacy of intramuscular administration. These results may have implications for altering pharmacokinetics and delivery of mABs used to treat non-infectious disorders. Cobb et al. demonstrate the utility of NHPs in studying pharmacokinetics and the efficacy of mABs and estimating thresholds for protection.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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