Next-Generation Monoclonal Antibody Blocks Malaria in Early Trial

An investigational monoclonal antibody called L9LS protected most recipients against malaria after controlled infection in a small phase 1 clinical trial, according to a report in the New England Journal of Medicine.

Currently, no antimalarial antibody is approved for clinical use. If successfully developed, adding antibodies to chemoprevention and vaccine therapies might substantially reduce malaria-related illness and deaths. The subcutaneous injection, taken once a season, could make antibodies cost-effective for treating high-risk groups including infants, young children, and pregnant women in regions where malaria is endemic, the report’s authors wrote.

In the trial, healthy adult volunteers in the US were exposed to bites from infected mosquitoes and monitored for malaria parasites in their blood for 21 days. Of the 17 volunteers injected with L9LS before malaria infection, only 2 developed parasitemia, whereas all 6 untreated volunteers did.

Of the L9LS-treated volunteers, 1 of 5 who received an intravenous dose of 1 mg per kilogram of body weight and 1 of 5 who received a dose of 5 mg per kilogram subcutaneously developed parasitemia. No participant who received an intravenous dose of 5 mg or 20 mg per kilogram subcutaneously developed parasitemia. No safety concerns emerged in the trial, which was funded and conducted by the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases.

Deemed a next-generation monoclonal antibody, L9LS performed substantially better than previous antimalarial antibodies in preclinical studies and in the current clinical study. The antibody itself has a higher affinity for its target protein, increasing its binding strength compared with earlier antibodies, while a gene modification helps resist lysosomal breakdown, increasing its and serum half-life.

L9LS works by interrupting the life cycle of Plasmodium falciparum, the most common and deadly malaria parasite. The antibody latches onto a protein in the parasite’s sporozoite stage, which infects humans through mosquito saliva. This effectively halts the infection by keeping the sporozoites from attaching to liver cells, preventing production of the merozoites that then infect and massively multiply in red blood cells. L9LS also promotes the cytolytic destruction of sporozoites.

"The current trial provides a proof of principle that prevention of malaria can be achieved with a next-generation monoclonal antibody, L9LS," the authors wrote. The authors reported that 2 phase 2 clinical trials are planned to test the efficacy of small subcutaneous doses in young children.

New Data on Heterologous COVID-19 Vaccine Combinations

Switching to a different COVID-19 vaccine after a first dose of the Sputnik V C1, ChAdOx1-S, or BBIBP-CorV vaccines can greatly increase immune response while maintaining safety, according to a study published in Cell Reports Medicine. The results provide information for mixing vaccine types in both primary vaccination and vaccine booster schedules, which is particularly important for middle- and low-income countries to strengthen vaccine programs, the authors wrote.

In the study, administering a messenger RNA (mRNA) vaccine dose between 34 and 80 days after a first dose with an inactivated virus or nonreplicating adenovirus vaccine boosted serum antibodies and neutralizing titers the most. Although the approach also increased vaccine-related adverse events, none were serious.

The study enrolled 1314 individuals in Argentina divided into 3 groups to receive their first vaccine dose: 669 received Sputnik V C1 (Gamaleya Institute), a non-replicating adenovirus vaccine; 448 received ChAdOx1-S (Oxford-AstraZeneca), also an adenovirus vaccine; and 197 received BBIBP-CorV (Sinopharm), an inactivated virus vaccine. The 3 first-dose cohorts were further divided into 15 groups that received as a second dose either the same vaccine or 1 of 5 different vaccines.

Before the second dose, levels of SARS-CoV-2 antispikes IgG antibodies and neutralizing antibody titers were similar among all study groups. In all 3 cohorts, antibody levels and neutralizing titers were lowest 14 and 21 days after a second dose of BBIBP-CorV and highest after a second dose of the mRNA vaccine mRNA-1273 (Moderna).

Combining the first dose with mRNA-1273 was superior to 2 doses of the same vaccine in all 3 cohorts, as was combining Sputnik V C1 with a first dose of ChAdOx1-S or BBIBP-CorV. Adding Sputnik V C2, ChAdOx1-S, or Ad5-nCoV (CanSino), an adenovirus vaccine, equaled or bettered the immune response following 2 doses of Sputnik V C1, as did adding Ad5nCoV in the ChAdOx1-S cohort.

Injection site pain was the most common local reaction, while headache and fever were the most common systemic reactions. No serious adverse events occurred in any study group.

Antibody Found in Mice Neutralizes SARS-CoV-2 and SARS-CoV-1

Researchers have identified an antibody that broadly neutralized all tested SARS-CoV-2 subvariants as well as SARS-CoV-1 in laboratory experiments and several SARS-CoV-2 variants of concern in mice. Because it targets a spike protein area that may be less affected by genetic variations, the newly discovered antibody could better retain potency against emerging SARS-CoV-2 subvariants and future coronaviruses, if developed into therapeutic products.
Most current SARS-CoV-2 therapeutic antibodies work by binding to proteins in the virus receptor binding domain (RBD) that target angiotensin-converting enzyme 2 (ACE2). This blocks the virus from attaching to ACE2 on host cell membranes. But as the virus has evolved, multiple genetic variations have altered the ACE2-binding proteins so much that most current antibodies no longer block them effectively.

By contrast, the recently discovered SW186 antibody binds to an outer RBD region that does not attach to ACE2. That this RBD area was conserved not only as SARS-CoV-2 evolved but also in the related SARS-CoV-1 suggests that it may control an important function likely to be conserved in future variants and SARS coronaviruses.

Researchers found SW186 by isolating a panel of SARS-CoV-2 antibodies from mice immunized with the viral spike protein. Laboratory tests showed that only SW186 and 1 other antibody neutralized all the SARS-CoV-2 variants tested, including HU-1, Alpha, Beta, Gamma, Lambda, Mu, and Omicron, though its potency against Omicron BA.2.12.1, BA.4, and BA.5 was reduced. SW186 also neutralized SARS-CoV-1.

SW186 greatly reduced SARS-CoV-2 Alpha, Beta, and Delta viral loads in the lungs of mice, and protected the lungs from viral damage and inflammatory cell infiltration. It also prevented body weight loss from the Delta variant.

“Further structure-based engineering of SW186 may lead to development of more broadly effective antibodies against the circulating and future SARS viruses,” the authors wrote in Science Immunology.

− Howard D. Larkin

Note: Source references are available through embedded hyperlinks in the article text online.