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THE LEADING SOURCE FOR PERIOPERATIVE HEALTH CARE NEWS

Monoclonal Antibody Therapies in COVID-19

Richard Simoneaux **Steven L. Shafer, MD**
Editor-in-Chief

Monoclonal antibodies are proteins made by cloning a single B cell (hence "*mono clonal*") into cultures that synthesize the antibody in sufficient quantities for research and, eventually, formulation into powerful medicine. Two Nobel Prizes have been awarded for monoclonal antibodies: to Jerne, Köhler, and Milstein in 1984 for discovering monoclonal antibodies, and to Allison and Honjo in 2018 for applying them to cancer therapy. Last year, noted Harvard biologist William Haseltine predicted that monoclonal antibodies would be the first therapy specifically developed for SARS-CoV-2 (asamonitor.pub/3dkUMfp).

He was right. On November 9, 2020, the U.S. FDA issued an emergency use authorization (EUA) for the investigational monoclonal antibody bamlanivimab (LY-CoV555, Eli Lilly) to treat mild-to-moderate cases of COVID-19 in adult and pediatric patients. Bamlanivimab is

Continued on page 7

Selecting an Anesthetic Technique for TAVI

Dibash Kumar Das

Transcatheter aortic valve replacement (TAVI) has become the standard of care for patients with severe symptomatic aortic stenosis. Since its introduction, the majority of TAVI procedures have been performed under general anesthesia. Initially developed as a less invasive alternative to surgical aortic valve replacement for high-risk or inoperable patients, its use has grown due to innovations in device design, smaller delivery systems, and increased procedural experience (*J Thorac Dis* 2018;10:S3588-94). These improvements in many aspects of the procedure have made TAVI even less invasive, which has led to a growing interest in "minimalist" TAVI (*Front Cardiovasc Med* 2018;5:96). An integral component of minimalist TAVI is the use of moderate sedation with

Continued on page 13

SPECIAL SECTION
Mentoring, Coaching, and Negotiation: Connecting With Purpose 26-32
Guest Editor: Solmaz Nabipour, MD

A Look Inside JPM 2021: Vaccination Industry Insights

Richard Simoneaux

The annual J.P. Morgan Healthcare Conference in San Francisco is a January tradition at which the leading biotech and pharmaceutical companies announce their major news and discoveries. At this year's virtual meeting, leaders from the pharmaceutical and biotech industries were focused on the COVID-19 pandemic. The first day of the conference, Monday, January 11, was devoted to current development of therapeutics. The following two days were focused on vaccines, including the upcoming second-wave of vaccines and logistical management of vaccine distribution. The *ASA Monitor* was in attendance and now brings you a front row seat to three of the meeting's enlightening panel discussions.

January 11, 2021: "In-Development COVID-19 Therapeutics"

In this first session of the conference, the panel members explained how the therapies currently being developed fit into the overall management of patients with COVID-19. Wendy Holman, CEO and Founder, Ridgeback Biotherapeutics, noted that COVID-19 is here to stay, and although it will change over time, there will never be a one-size-fits-all approach to treatment. "It's important to have multiple shots on goal, and thus potential combination therapies," she said. Julie Kim, President of the Plasma-Derived Therapies Business Unit, Takeda, agreed that the multiple shots on goal concept is critical given our limited understanding

Continued on page 24

PERIODICALS

In the Know: Monoclonal Antibody Therapies

Continued from page 1

an antibody directed against the SARS-CoV-2 spike protein. Monoclonal antibodies tend to have unpronounceable names, but the "mab" at the end of the name stands for "monoclonal antibody."

Bamlanivimab monotherapy

A preplanned interim analysis of the BLAZE-1 randomized controlled trial looked at both virologic and clinical outcomes in 452 outpatients after treatment with bamlanivimab, a SARS-CoV-2-spike protein-targeting monoclonal antibody (*N Engl J Med* 2021;384:229-37). Patients were randomized to one of four treatment arms: (700 mg, 2,800 mg, 7,000 mg, or placebo). Viral load at 11 days, measured by the cycle-threshold of the RT-PCR assay, was the primary endpoint. The study also looked at symptom score and emergency department visits or hospitalizations. To the authors' credit, only viral load, the primary outcome variable, was tested for statistical significance.

While the three antibody doses decreased viral load, only the 2,800-mg dose produced a statistically significant drop in cycle threshold (P=0.02). The 7,000-mg dose performed the worst (P=0.7). Only 1.6% of patients who received bamlanivimab required hospitalization, while 6.3% of those receiving placebo required hospitalization. Additionally, the clinical burden, assessed by a survey of multiple symptoms, resolved more quickly in those receiving bamlanivimab.

The interim analysis led to the EUA for bamlanivimab on November 9 last year, the first monoclonal therapy approved for COVID-19. The EUA authorized bamlanivimab for patients testing positive for SARS-CoV-2 who are 12 years or older and at risk for progressing to severe COVID-19 and/or hospitalization.

Bamlanivimab/etesevimab cocktail

The BLAZE-1 randomized controlled trial continued with bamlanivimab 2,800 mg combined with etesevimab 2,800 mg in an antibody "cocktail." Etesevimab is another monoclonal antibody directed against the spike protein. As before, the primary endpoint was the viral load at day 11, with secondary endpoints including hospitalizations and clinical symptoms.

The combination antibody cocktail significantly decreased viral load on day 11 when compared with placebo (P = 0.01)(JAMA January 2021). Only 1% of patients with the monoclonal cocktail required hospitalization, compared with 6% of patients in the placebo group (P=0.049). Treatment with the monoclonal cocktail reduced symptoms from one week through 22 days after, compared with patients in the control group, but this only reached statistical significance (P<0.05) on day 11. The only adverse event in any patient was a urinary tract infection, which was considered unrelated to the study drug.

On February 9, 2021, the FDA issued an EUA for the co-administration of bamlanivimab and etesevimab in a monoclonal cocktail to treat mild-to-moderate COVID-19 in those age 12 or older who are at risk for progression to severe COVID-19. The EUA also allowed the drugs to be infused over just 20 minutes, significantly faster than the 60 minutes required by the initial EUA.

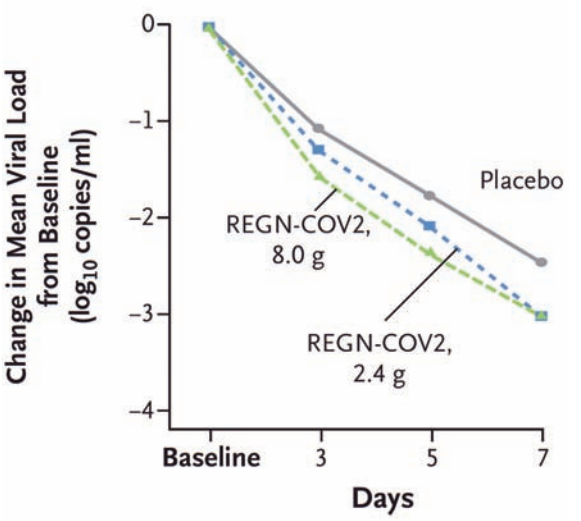

Figure 1: Viral Load over Time in the Overall Population

Source: Weinreich DM, Sivapalasingam S, Norton T. REGN-COV2, a neutralizing antibody cocktail, in outpatients with covid-19. *N Engl J Med.* 2021;384(3):238-51.

REGN-COV2

Regeneron, a competitor of Lilly, actively pursued a cocktail of two monoclonal antibodies, casirivimab and imdevimab, after seeing promising results in rhesus monkeys (*Science* 2020;370:1110-5). Like Lilly, they anticipated that a two-antibody cocktail would make it more difficult for resistant variants to emerge. The rationale is the same as our use of a three-drug regimen for tuberculosis to prevent emergence of resistant strains of TB. Their two antibodies were also directed at the spike protein. In a double-blinded RCT, Regeneron compared placebo, 2.4 g of REGN-COV2, and 8.0 g of REGN-COV2 (*N Engl J Med* 2021;384:238-51). Similar to the BLAZE-1 trial, their primary outcome variable was viral load (at seven days). The prespecified clinical endpoint was the percent of patients with at least one COVID-19 related medical visit through day 29.

As shown in Figure 1, both doses of REGN-COV2 decreased viral load compared with placebo. Six percent of patients in the placebo group required a medical visit, while only 3% in the combined treatment groups required a visit. There was no difference in the safety analysis between treatment and control patients.

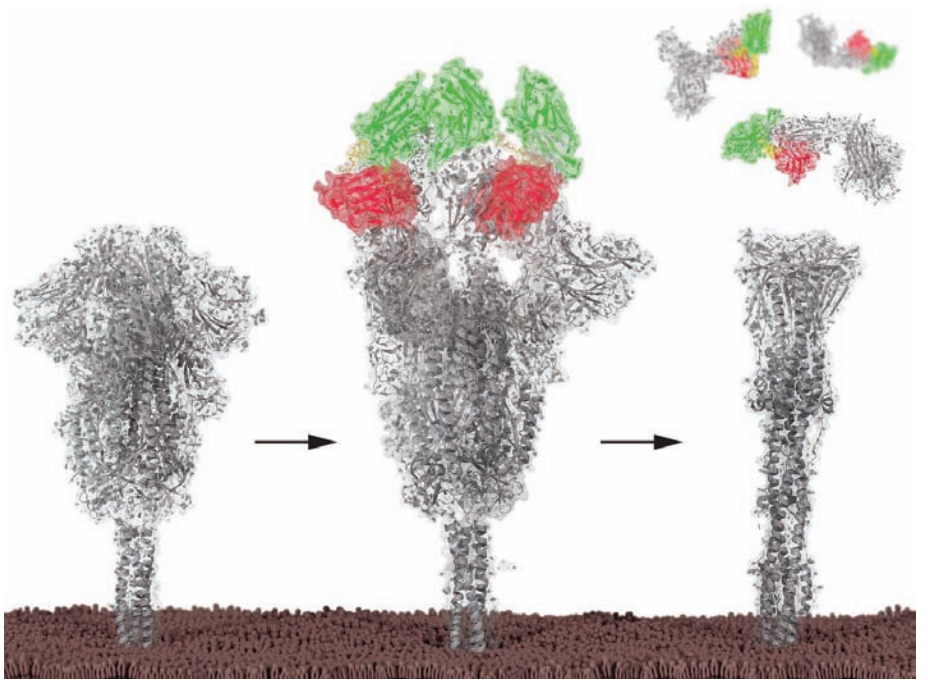

Figure 2: Bivalent nanobodies neutralize by inducing postfusion conformation of the SARS-CoV-2 spike.

On virions, SARS-CoV-2 spike trimers are mostly in an inactive configuration with all RBDs in the down conformation (left). Binding of bivalent nanobody VE stabilizes the spike in an active conformation with all RBDs up (middle), triggering premature induction of the postfusion conformation, which irreversibly inactivates the spike protein (right).

Source: Koenig PA, Das H, Liu H, et al. Structure-guided multivalent nanobodies block SARS-CoV-2 infection and suppress mutational escape. *Science.* 2021;371:eabe6230.

Additional N=1 evidence was accumulated when President Trump was treated with REGN-COV2 at Walter Reed hospital following his diagnosis of COVID-19.

Based on the accumulated evidence, on November 21, the FDA issued an EUA for the monoclonal antibody cocktail of casirivimab and imdevimab (REGN-COV2, Regeneron) to treat mild-to-moderate COVID-19 in patients 12 years or older who were at risk for progressing to severe COVID-19.

Future directions

The two approved antibody cocktails, impressive as they are, are only the first steps in creating antibodies against SARS-CoV-2. Using an approach called "directed-evolution," scientists engineered an antibody, ADG-2, that shows strong affinity to the receptor-binding domain of the spike protein (*Science* January 2021). ADG-2 is not specific to SARS-CoV-2, but is highly efficient against the all SARS betacoronaviruses. It also binds avidly to the N501Y mutation in the rapidly spreading B.1.1.7 variant.

The authors noted, "ADG-2 binds to a highly conserved motif {in the spike protein} through a distinct angle of approach…. This epitope may represent an 'Achilles' heel' for clade 1 sarbecoviruses…. ADG-2 represents a promising candidate for the prevention and treatment of not only COVID-19, but also future respiratory diseases caused by pre-emergent SARS-related CoVs." If subsequent studies bear this out, ADG-2 could be stockpiled as an "off-the-shelf" monoclonal antibody the next time a betacoronavirus jumps into the human population.

"Single-domain antibodies" are super-compact antibodies (asamonitor.pub/3u04RVj). They are typically a peptide chain of about 110 amino acids but have similar ability to bind antigens as conventional antibodies. Their small size allows them to reach antigens that conventional antibodies are too bulky to reach. We don't make these – they were first identified in camels. However, we can synthesize them in a lab.

There are many potential benefits to single domain antibodies: 1) they can bind to antigens (e.g., pieces of the spike protein) that conventional antibodies are too bulky to reach, 2) they are really cheap to make, 3) they are stable so special storage and handling isn't required, and 4) they can be absorbed through the lungs and administered with a simple nebulizer. Because the hard-to-get-to targets of single-domain antibodies aren't visible to our human immune system, there isn't strong selection pressure for mutations.

Scientists have created several single-domain antibodies that have very strong binding to highly conserved portions of the SARS-CoV-2 spike protein, with no

Continued on page 8

Richard Simoneaux is a freelance writer with an MS in organic chemistry from Indiana University. He has more than 15 years of experience covering the pharmaceutical industry and an additional seven years as a laboratory-based medicinal chemist.

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Learning From Others: A Case Report from the Anesthesia Incident Reporting System

Case 2021-4: Measure Twice, Cut Once

Laboring patient received epidural for labor analgesia. After epidural placement and dosing, patient became hypotensive. Ephedrine and NeoSynephrine were then used to treat the hypotension. After NeoSynephrine administration, the patient became hypertensive and was reporting chest and arm pain and headache. Also, during this time period fetal distress was noted and patient underwent emergent cesarean section under general anesthesia. Patient and infant did well. Apgars were 8,9 but cord gas did show acidosis. After event, it was noted that NeoSynephrine was only diluted to 1 mg/ml instead of 100 mcg/ml.

Contributing factors: *NeoSynephrine must be diluted twice – to 1 mg/ml, then to 100 mcg/ml.*

Hurrying due to symptomatic hypotension in laboring parturient.

Multiple health care workers and family at bedside leading to distraction.

Lessons learned: *Slow down when diluting medication and double check dilution.*

Minimize distractions during preparation and administration of medication.

Double dilution of vasoconstrictors has a long history in anesthesia, with virtually every anesthesia provider at some point performing this task. Like many tasks in anesthesia, this one is not complex. Taking a 10 mg/mL to a 0.1 mg/mL solution (100 micrograms per mL) via a two-step dilution of 1 mg/mL to 0.1 mg/mL and then, with nine more mL of saline, to a 0.01 mg/mL (or 100 mcg/mL) is straightforward. The steps are linear and the same every time, and the error of omitting the second dilution falls into what James Reason defines as a skill-based error, with a slip or lapse in a routine that we have done many times before (Human Error. 1990). In Dr. Reason's framework of cognitive errors, skill-based errors are joined by rules-based errors and knowledge-based errors.

As shown in the table, Kahneman divides our day-to-day cognitive processes (and actions) into fast and slow thinking (Thinking, Fast and Slow. 2011), while Stanovich and West use the terms System I (fast) and System II (slow) (*Behav Brain Sci* 2000;23:645-726). System I thinking and actions are associative, unconscious, effortless, and come after many repetitions of a task or multiple exposures to a certain pattern (if bradycardic, give atropine); System I includes Reason's skill based and rule-based errors. System II thinking or actions are slow and reflective, deductive, conscious and effortful (first attempts at intubation). It is no wonder that humans much prefer to live in the world where our stored schema run subconsciously, even as we carry on conversations, or monitor vital signs. However, each of these basic types of thinking are inherently at risk for specific errors. For System I thinking common errors include that we run a schema at the wrong time (give atropine for bradycardia caused by electrocautery interference of a pacemaker), or that the schema is interrupted mid-stream, and when we return to it, we either enter a step too early or too late, omitting a step. In the case of severe hypertension noted above, the second step, that of diluting the 1 mg/mL solution once more, was omitted.

Although there is not a plethora of case reports of this type of error in the literature, virtually every provider of some experience knows of a local case or two of errors in dilution or has been called to assist when an error has occurred and the team must manage severe hypertension or, in this case, significant fetal distress. In pediatrics, the dangers are more prevalent and often more serious due to the need for dilution of nearly all medications and the narrow therapeutic range in our tiniest patients. In a study by Avidan, faculty and residents were asked to calculate the correct dilution for a number of

APSF NEWSLETTER Spring 2010 PAGE 7

Conference Leads to Consensus Recommendations

"Medication Safety," From Preceding Page

Small Groups, Big Assignments

Predictably, each of the 4 group breakout sessions: **Standardization, Technology, Pharmacy/Prefilled/Premixed, and Culture,** generated intense debate. There was a specific assignment to generate up to 3 primary actionable recommendations that could produce "predictable prompt improvement" in operating room medication safety. There was also the requirement to balance the often contradictory considerations of the clearly ideal top-priority beneficial measures vs. the realistic practicality of potential for implementation in the short-term future. Thus, the discussions involved a great many back-and-forth swings of argument and opinion.

The Standardization Group, led by **Patricia A. Kapur, MD,** APSF Executive Committee member, considered what degree of standardization would be achievable for which components of the operating room medication process and how that could be accomplished. The Technology Group, led by **George A. Shapiro,** APSF executive vice president, eventually decided to leave the issue of configuration of medication containers to the Standardization Group and focus on hardware and software that could prevent drug errors. The Pharmacy Group, led by **Sorin J. Brull, MD,** chair of the APSF Scientific Evaluation Committee, struggled with the balance of roles between the anesthesia professional in the operating room in real time and the related supporting pharmacist as far as maximizing safety of medication procedures. The Culture Group, led by **Robert C. Morell, MD,** editor of the *APSF Newsletter,* debated what would be the best target mindset to promote operating room medication safety and then how best to achieve that goal.

Consensus Building

After the breakout sessions the 4 groups reassembled in the main meeting room for the final

See "Medication Safety," Next Page

Table 1:
Consensus Recommendations for Improving Medication Safety in the Operating Room

Standardization

1. High alert drugs (such as phenylephrine and epinephrine) should be available in standardized concentrations/diluents prepared by pharmacy in a ready-to-use (bolus or infusion) form that is appropriate for both adult and pediatric patients. Infusions should be delivered by an electronically-controlled smart device containing a drug library.
2. Ready-to-use syringes and infusions should have standardized fully compliant machine–readable labels.
3. *Additional Ideas:*
   a. Interdisciplinary and uniform curriculum for medication administration safety to be available to all training programs and facilities.
   b. No concentrated versions of any potentially lethal agents in the operating room.
   c. Required read-back in an environment for extremely high alert drugs such as heparin.
   d. Standardized placement of drugs within all anesthesia workstations in an institution.
   e. Convenient required method to save all used syringes and drug containers until case concluded.
   f. Standardized infusion libraries/protocols throughout an institution.
   g. Standardized route-specific connectors for tubing (IV, arterial, epidural, enteral).

Technology

1. Every anesthetizing location should have a mechanism to identify medications before drawing up or administering them (bar code reader) and a mechanism to provide feedback, decision support, and documentation (automated information system).
2. *Additional Ideas:*
   a. Technology training and device education for all users, possibly requiring formal certification.
   b. Improved and standardized user interfaces on infusion pumps.
   c. Mandatory safety checklists incorporated into all operating room systems.

Pharmacy/Prefilled/Premixed

1. Routine provider-prepared medications should be discontinued whenever possible.
2. Clinical pharmacists should be part of the perioperative/operating room team.
3. Standardized pre-prepared medication kits by case type should be used whenever possible.
4. *Additional Ideas:*
   a. Interdisciplinary and uniform curriculum for medication administration safety for all anesthesia professionals and pharmacists.
   b. Enhanced training of operating room pharmacists specifically as perioperative consultants.
   c. Deployment of ubiquitous automated dispensing machines in the operating room suite (with communication to central pharmacy and its information management system).

Culture

1. Establish a *"just culture"* for reporting errors (including near misses) and discussion of lessons learned.
2. Establish a culture of education, understanding, and accountability via a required curriculum and CME and dissemination of dramatic stories in the *APSF Newsletter* and educational videos.
3. Establish a culture of cooperation and recognition of the benefits of STPC within and between institutions, professional organizations, and accreditation agencies.

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Consensus Recommendations for Improving Medication Safety in the Operating Room (*APSF Newsletter* 2010;25).

In the Know: Monoclonal Antibody Therapies

Continued from page 7

diminution of activity against known variants (*Science* February 2021). The single domain antibodies are able to lock the spike protein in an "active" configuration, which results in the receptor binding domain cleaving from the protein as shown in Figure 2. The result is an inactive, noninfectious spike.

Quoting the authors: "Perhaps, in the future, a positive rapid SARS-CoV-2 test outcome will go hand in hand with an easily administered, affordable, subcutaneous injection or nebulized inhalation of an antibody targeting highly conserved epitopes not recognized by the human immune system." In other words, as soon as you have a positive test, you are given a nebulized treatment rendering it impossible for the COVID-19 to progress.

Why are deaths so high?

Monoclonal antibodies have been available since late November. Since effective therapy has been available, why did COVID-19 deaths surge to new peaks in January? One reason, of course, is that cases surged because of SARS-CoV-2 seasonality as well as the superspreading events of the Thanksgiving and Christmas holidays. However, even with surging cases, shouldn't deaths have decreased dramatically with the availability of these cocktails?

This hasn't been well studied, but several explanations have been floated in the media as to why deaths are surging and antibody cocktails sit, unused, on pharmacy shelves (*N Engl J Med* 2021;384:289-91; asamonitor.pub/2N3kSZZ):

1. Treatment for COVID-19 is advancing so fast that many clinicians are not aware that these are available.
2. There is a mistaken belief that these are for inpatient use. That may arise, in part, because the approved cocktails must be given by I.V. infusion. However, the intent is for the drugs to be administered to outpatients early in the course of the disease.
3. The reason to give the cocktails early in therapy is that they must be given before the immune system goes haywire. As COVID-19 progresses from moderate to severe disease, end-organ damage changes from viral-induced to autoimmune injury. At that point, decrease viral load is of limited benefit.

William Haseltine was right: monoclonal antibodies have been quickly developed. They have the potential to radically change therapy. As always, science has progressed faster than clinical medicine. Monoclonal antibody cocktails should be considered on the initial presentation of any patient with COVID-19 at risk for serious illness. ■