Author Q&A: Intravenous Immunoglobulin for Treatment of COVID-19 in Select Patients

Dr. George Sakoulas is an infectious diseases clinician at Sharp Memorial Hospital in San Diego and professor of pediatrics at the University of California, San Diego School of Medicine. He was the lead investigator in a study published in the May/June 2022 issue of JCOM that found that, when allocated to the appropriate patient type, intravenous immunoglobulin can reduce hospital costs for COVID-19 care.[1] *He joined JCOM's Editor-in-Chief, Dr. Ebrahim Barkoudah, to discuss the study's background and highlight its main findings.*

The following has been edited for length and clarity.

Dr. Barkoudah Dr. Sakoulas is an investigator and a clinician, bridging both worlds to bring the best evidence to our patients. We're discussing his new article regarding intravenous immunoglobulin in treating non-ventilated COVID-19 patients with moderate-to-severe hypoxia. Dr. Sakoulas, could you please share with our readers the clinical question your study addressed and what your work around COVID-19 management means for clinical practice?

Dr. Sakoulas Thank you. I'm an infectious disease physician. I've been treating patients with viral acute respiratory distress syndrome for almost 20 years as an ID doctor. Most of these cases are due to influenza or other viruses. And from time to time, anecdotally and supported by some literature, we've been using IVIG, or intravenous immunoglobulin, in some of these cases. And again, I can report anecdotal success with that over the years.

So when COVID emerged in March of 2020, we deployed IVIG in a couple of patients early who were heading downhill. Remember, in March of 2020, we didn't have the knowledge of steroids helping, patients being ventilated very promptly, and we saw some patients who made a turnaround after treatment with IVIG. We were able to get some support from an industry sponsor and perform and publish a pilot study, enrolling patients early in the pandemic. That study actually showed benefits, which then led the sponsor to fund a phase 3 multicenter clinical trial. Unfortunately, a couple of things happened. First, the trial was designed with the knowledge we had in April of 2020, and again, this is before steroids, before we incorporated proning patients in the ICU, or started ventilating people early. So there were some management changes and evolutions and improvements that happened. And second, the trial was enrolling a very broad repertoire of patients. There were no age limitations, and the trial, ultimately a phase 3 multicenter trial, failed to meet its endpoint.

There were some trends for benefit in younger patients, and as the trial was ongoing, we continued to evolve our knowledge, and we really honed it down to seeing a benefit of using IVIG in patients with COVID with specific criteria in mind. They had to be relatively younger patients, under 65, and not have any major comorbidities. In other words, they weren't dialysis patients or end-stage disease patients, heart failure patients, cancer or malignancy patients. So, you know, we're looking at the patients under 65 with obesity, diabetes, and hypertension, who are rapidly declining, going from room air to BiPAP or high-flow oxygen in a short amount of time. And we learned that when using IVIG early, we actually saw patients improve and turn around.

What this article in JCOM highlighted was, number one, incorporating that outcome or that patient type and then looking at the cost of hospitalization of patients who received IVIG versus those that did not. There were 2 groups that were studied. One was the group of patients in that original pilot trial that I discussed who were randomized to receive 1 or the other prospectively; it was an unblinded randomized study. And the second group was a matched case-control study where we had

patients treated with IVIG matched by age and comorbidity status and level of hypoxia to patients that did not receive IVIG. We saw a financial benefit in shortening or reducing hospitalizations, really coming down to getting rid of that 20% tail of patients that wound up going to the ICU, getting intubated, and using a high amount of hospital resources that would ramp up the cost of hospitalization. We saw great mitigation of that with IVIG, and even with a small subset of patients, we were able to show a benefit.

Dr. Barkoudah Any thoughts on where we can implement the new findings from your article in our practice at the moment, knowing we now have practice guidelines and protocols to treat COVID-19? There was a tangible benefit in treating the patients the way you approached it in your important work. Could you share with us what would be implementable at the moment?

Dr. Sakoulas I think, fortunately, with the increasing host immunity in the population and decreased virulence of the virus, perhaps we won't see as many patients of the type that were in these trials going forward, but I suspect we will perhaps in the unvaccinated patients that remain. I believe one-third of the United States is not vaccinated. So there is certainly a vulnerable group of people out there. Potentially, an unvaccinated patient who winds up getting very sick, the patient who is relatively young—what I'm looking at is the 30- to 65-year-old obese, hypertensive, or diabetic patient who comes in and, despite the steroids and the antivirals, rapidly deteriorates into requiring high-flow oxygen. I think implementing IVIG in that patient type would be helpful. I don't think it's going to be as helpful in patients who are very elderly, because I think the mechanism of the disease is different in an 80-year-old versus a 50-year-old patient. So again, hopefully, it will not amount to a lot of patients, but I still suspect hospitals are going to see, perhaps in the fall, when they're expecting a greater number of cases, a trickling of patients that do meet the criteria that I described.

Dr. Barkoudah JCOM's audience are the QI implementers and hospital leadership. And what caught my eye in your article is your perspective on the pharmacoeconomics of treating COVID-19, and I really appreciate your looking at the cost aspect. Would you talk about the economics of inpatient care, the total care that we provide now that we're in the age of tocilizumab, and the current state of multiple layers of therapy?

Dr. Sakoulas The reason to look at the economics of it is because IVIG—which is actually not a drug, it's a blood product—is very expensive. So, we received a considerable amount of administrative pushback implementing this treatment at the beginning outside of the clinical trial setting because it hadn't been studied on a large scale and because the cost was so high, even though, as a clinician at the bedside, I was seeing a benefit in patients. This study came out of my trying to demonstrate to the folks that are keeping the economics of medicine in mind that, in fact, investing several thousand dollars of treatment in IVIG will save you cost of care, the cost of an ICU bed, the cost of a ventilator, and the cost even of ECMO, which is hugely expensive.

If you look at the numbers in the study, for two-thirds or three-quarters of the patients, your cost of care is actually greater than the controls because you're giving them IVIG, and it's increasing the cost of their care, even though three-quarters of the patients are going to do just as well without it. It's that 20% to 25% of patients that really are going to benefit from it, where you're reducing your cost of care so much, and you're getting rid of that very, very expensive 20%, that there's a cost savings across the board per patient. So, it's hard to understand when you say you're losing money on three-quarters of the patients, you're only saving money on a quarter of the patients, but that cost of saving on that small subset is so substantial it's really impacting all numbers.

Also, abandoning the outlier principle is sort of an underlying theme in how we think of things. We tend to ignore outliers, not consider them, but I think we really have to pay attention to the more extreme cases because those patients are the ones that drive not just the financial cost of care. Remember, if you're down to 1 ventilator and you can cut down the use of scarce ICU resources, the cost is sort of even beyond the cost of money. It's the cost of resources that may become scarce in some settings. So, I think it speaks to that as well.

A lot of the drugs that we use, for example, tocilizumab, were able to be studied in thousands of patients. If you

look at the absolute numbers, the benefit of tocilizumab from a magnitude standpoint—low to mid twenties to high twenties—you know, reducing mortality from 29% to 24%. I mean, just take a step back and think about that. Even though it's statistically significant, try telling a patient, "Well, I'm going to give you this treatment that's going to reduce mortality from 29% to 24%." You know, that doesn't really change anything from a clinical significance standpoint. But they have a *P* value less than .05, which is our standard, and they were able to do a study with thousands of patients. We didn't have that luxury with IVIG. No one studied thousands of patients, only retrospectively, and those retrospective studies don't get the attention because they're considered biased with all their limitations. But I think one of the difficulties we have here is the balance between statistical and clinical significance. For example, in our pilot study, our ventilation rate was 58% with the non-IVIG patients versus 14% for IVIG patients. So you might say, magnitude-wise, that's a big number, but the statistical significance of it is borderline because of small numbers.

Anyway, that's a challenge that we have as clinicians trying to incorporate what's published—the balancing of statistics, absolute numbers, and practicalities of delivering care. And I think this study highlights some of the nuances that go into that incorporation and those clinical decisions.

Dr. Barkoudah Would you mind sharing with our audience how we can make the connection between the medical outcomes and pharmacoeconomics findings from your article and link it to the bedside and treatment of our patients?

Dr. Sakoulas One of the points this article brings out is the importance of bringing together not just level 1A data, but also small studies with data such as this, where the magnitude of the effect is pretty big but you lose the statistics because of the small numbers. And then also the patients' aspects of things. I think, as a bedside clinician, you appreciate things, the nuances, much sooner than what percolates out from a level 1A study. Case in point, in the sponsored phase 3 study that we did, and in some other studies that were prospectively done as well, these studies of IVIG simply had an enrollment of patients that was very broad, and not every patient benefits from the same therapy. A great example of this is the sepsis trials with Xigris and those types of agents that failed. You know, there are clinicians to this day who believe that there is a subset of patients that benefit from agents like this. The IVIG story falls a little bit into that category. It comes down to trying to identify the subset of patients that might benefit. And I think we've outlined this subset pretty well in our study: the younger, obese diabetic or hypertensive patient who's rapidly declining.

It really brings together the need to not necessarily toss out these smaller studies, but kind of summarize everything together, and clinicians who are bedside, who are more in tune with the nuances of individual decisions at the individual patient level, might better appreciate these kinds of data. But I think we all have to put it together. IVIG does not make treatment guidelines at national levels and so forth. It's not even listed in many of them. But there are patients out there who, if you ask them specifically how they felt, including a friend of mine who received the medication, there's no question from their end, how they felt about this treatment option. Now, some people will get it and will not benefit. We just have to be really tuned into the fact that the same drug does not have the same result for every patient. And just to consider this in the high-risk patients that we talked about in our study.

Dr. Barkoudah While we were prepping for this interview, you made an analogy regarding clinical evidence along the lines of, "Do we need randomized clinical trials to do a parachute-type of experiment," and we chatted about clinical wisdom. Would you mind sharing with our readers your thoughts on that?

Dr. Sakoulas Sometimes, we try a treatment and it's very obvious for that particular patient that it helped them. Then you study the treatment in a large trial setting and it doesn't work. For us bedside clinicians, there are some interventions sometimes that do appear as beneficial as a parachute would be, but yet, there has never been a randomized clinical trial proving that parachutes work. Again, a part of the challenge we have is patients are so different, their immunology is different, the pathogen infecting them is different, the time they present is different. Some

present early, some present late. There are just so many moving parts to treating an infection that only a subset of people are going to benefit. And sometimes as clinicians, we're so nuanced, that we identify a specific subset of patients where we know we can help them. And it's so obvious for us, like a parachute would be, but to people who are looking at the world from 30,000 feet, they don't necessarily grasp that because, when you look at all comers, it doesn't show a benefit.

So the problem is that now those treatments that might help a subset of patients are being denied, and the subset of patients that are going to benefit never get the treatment. Now we have to balance that with a lot of stuff that went on during the pandemic with, you know, ivermectin, hydroxychloroquine, and people pushing those things. Someone asked me once what I thought about hydroxychloroquine, and I said, "Well, somebody in the lab probably showed that it was beneficial, analogous to lighting tissue paper on fire on a plate and taking a cup of water and putting the fire out. Well, now, if you take that cup of water to the Caldor fire that's burning in California on thousands of acres, you're not going to be able to put the fire out with that cup of water." So while it might work in the lab, it's truly not going to work in a clinical setting. We have to balance individualizing care for patients with some information people are pushing out there that may not be necessarily translatable to the clinical setting.

I think there's nothing better than being at the bedside, though, and being able to implement something and seeing what works. And really, experience goes a long way in being able to individually treat a patient optimally.

Dr. Barkoudah Thank you for everything you do at the bedside and your work on improving the treatment we have and how we can leverage knowledge to treat our patients. Thank you very much for your time and your scholarly contribution. We appreciate it and I hope the work will continue. We will keep working on treating COVID-19 patients with the best knowledge we have.

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Reference

1. Poremba M, Dehner M, Perreiter A, et al. Intravenous immunoglobulin in treating nonventilated COVID-19 patients with moderate-to-severe hypoxia: a pharmacoeconomic analysis. *J Clin Outcomes Manage*. 2022;29(3):123-129. doi:10.12788/jcom.0094