

Q & A: The Rheumatologist's Role in Covid-19

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Dr. Earl Silverman (ES): Hello, this is Earl Silverman, Editor-in-Chief of *The Journal of Rheumatology*, welcoming you to this Podcast that I believe is prescient, and I think you will find both informative and interesting.

As I am doing this interview at home to conform to social isolation, I hope all are doing well and staying healthy in these unusual times, as a result of the SARS-CoV-2 virus pandemic.

Today, I am pleased to have as my guests Drs. Randy Cron and Winn Chatham from the University of Alabama at Birmingham. They are the authors of an article entitled, "The Rheumatologist's Role in COVID-19". This article is available at the website at The Journal of Rheumatology's website: jrheum.org.

So Randy and Winn, thank you for joining me and taking time from your busy schedules. First, could briefly summarize the findings in your article.

Dr. Randy Cron (RC): I can start out and Winn can chime in. Since the early reports coming out of China, some of the clinical features that primarily a lot of the laboratory features in the patients they were reporting on with hospitalizable sick COVID-19 infections appeared to have cytokine storm syndrome.

This included elevated serum ferritin, elevated soluble CD25, IL-3 receptor alpha chain, elevated liver enzymes, coagulopathic features, D dimers, and elevated LDH. Some of these patients are going onto multiorgan failure in addition to developing acute respiratory distress syndrome. And so, it made sense to us that as rheumatologists, we should, number one, be helping to diagnose cytokine storms syndrome, if it's part of what's going on with hospitalized patients with COVID-19. And then potentially, what could we offer in terms of therapy?

Dr. Winn Chatham (WC): Yeah. And I would just add that this pattern of what's seen has been seen with previous viral epidemics as a similar pattern that was seen with the Ebola outbreaks, as well as the previous coronavirus outbreaks with SARS and MERS. Similar patterns have been seen in these other viruses that have had significant morbidity and mortality. So, the footprints of cytokine storm were there for those syndromes as well as other syndromes in which other situations where we see the syndrome. So very high likelihood that that's what's going on with a lot of the severely ill current coronaviruses patients.

ES: Make sense and really brings us to part of the other question of why you felt this was important to be recognized early.

In your article said: "Once hospitalized, for some patients, death can occur within a few days, many with

adult respiratory distress syndrome (ARDS), and some with multiorgan dysfunction syndrome (MODS).”

So what’s your hypothesis for this particular virus? You mentioned some other viruses, but what do you think’s going on here? Because you said some, but certainly not all viruses do this.

WC: Well, the question is why would we be seeing us with this particular virus and unknown at this point that with the Ebola virus, we knew that that virus tended to preferentially infect macrophages and dendritic cells, and could trigger significant cytokine release by those cell populations.

And that’s probably why this was one of the major reasons this was probably seen in patients infected with Ebola. Now what the mechanism is with the COVID-19 virus, we’re not sure.

I mean, it’s possible that when the virus infects these cells in the lung that they’re the angiotensin-converting enzyme on their surface. Perhaps when the virus enters those cells, similar mechanisms might be engaged to where those cells or ones adjacent to them might be elaborating lots of cytokines, but the exact mechanism behind why these viruses induce this still hasn’t been elucidated either with the SARS and MERS epidemics or thus far with this one.

RC: I think it’s also important to point out, as we’re learning as we go with this virus, that this has features of some of our more familiar cytokine storm syndromes, including macrophage activation syndrome, which we see in our lupus patients or our Still disease patients, for example. But it’s not identical.

It does really target the lungs in a bad way. And maybe that’s because it goes deep into the lung to start, and even ferritin values, which are clearly elevated in the thousands, tend not to be in the tens or hundreds of thousands. And maybe that’s because they suffer the lung disease so much initially, they don’t get that far.

But some of them currently develop multiorgan failure and there’s now some evidence that maybe up to 15% have significant central nervous system involvement that’s likely associated with the cytokine storm as well.

ES: As you said, there are certain features that we’re familiar with, with more common rheumatic diseases leading to what we call MAS, but I guess that’s just semantics. We were used to MAS, cytokine storm.

But my next question really is, who should be screened? How do you decide who should be screened? What’s your recommendations of the initial screening tests?

RC: I think screening early is going to be important, and early to me means the instance someone thinks you’re sick enough to be hospitalized. And I realize that’s a moving target in the current day when our hospitals are being overwhelmed in some places. But if you’re generally sick enough to be hospitalized, I

think you need to be screened at that point and hopefully treated early enough if it looks like you have a cytokine storm.

And the simple, I mean, people are going to likely get a complete blood count and you can look for lymphopenia, which seems to be really common in this particular outbreak, as well as a trend towards thrombocytopenia. It may not be there in the initial one, but it tends to drop, like we see in other cytokine storms.

But I think the serum ferritin value, anything essentially over 600 or 700 is kind of our guess cutoff, should get your attention and nanograms per milliliter, should wake you up. Then at that point, you're going to get other labs that can help confirm or deny your suspicion for a cytokine storm, and those will include things like D dimers, lactate dehydrogenase, fibrinogen levels, elevated liver enzymes, to name a few.

WC: These patients also have a very high CRP as well, so that's oftentimes can be a tip off as well.

It's not specific for cytokine storm syndrome. If you see CRP levels greater than 150, 200, I think you start worrying, so you want to test that can be turned around quite quickly. And I think certainly the LDH, D dimer, CRP, most hospitals can do a ferritin on the same-day basis.

So if you get that combination as labs back then, I think the likelihood of this being present tends to be fairly high.

ES: In your article, you do list different diagnostic criteria for cytokine storms because they're all different.

I think one of the errors that we make and/or imposed upon us, however we want to put it, is that they don't meet the criteria for the classic HLH, which is again the classic one associated with genetic defect with cytokine storm.

And I think it is very important you mentioned something about a ferritin to ESR ratio.

And the other thing I want you to comment on, certainly, on the internet and other places, rumors that the ferritin isn't sky high, like 20, 30, 40 hundred thousand.

Would you like to comment on that?

RC: Sure, the ferritin sedimentation rate ratio has come up a couple of papers now because the ferritin tends to climb as you're getting sicker with the cytokine storm. And the erythrocyte sedimentation rate may start out high because you're clearly inflamed, and one of the drivers of that is fibrinogen binding to the red cells to make them fall quicker.

But if there's a coagulopathic process that's going on, which there typically is and why we see elevated D dimers, for example, then the fibrinogen gets consumed, and therefore, the sedimentation rate starts to drop.

So, a ratio, and no one knows what the cutoff will be for COVID-19, and you could probably just go the ferritin alone to tell you the truth at this point, but a ratio certainly over 20 would get my attention, and the threshold may be even lower than that.

WC: Yeah, and to the point you made earlier, the criteria don't necessarily apply across all different diseases, so there's criteria for cytokine storm in patients that have systemic-onset JIA that are fairly well validated. Those criteria may not be equally applicable to cytokine storms triggered by viral infections.

There's H-score, which is a little bit more broad in terms of applicability, but again, when those criteria were developed, the population was a bit heavily weighted toward patients with underlying malignancies, and some of the points that are assigned to that score involve tests and pathology findings that you can't turn around real quickly when you're trying to evaluate a patient that can be critically ill and deteriorate quite quickly in a 24- to 48-hour time frame that's being seeing some of these patients.

So coming up with some adaptive criteria may help. In some of the reviews we've done here over the years, applying some adaptation to the HLH 2004 criteria may be helpful in terms of a useful algorithm to identify these patients, where if you have fever, hyperferritinemia, and perhaps three of either thrombocytopenia, leukemia, LDH, elevated D dimer, or AST/ALT elevations — that can often be a useful criteria that's fairly sensitive and specific for identifying these patients.

ES: Thank you, I really want the listeners to read the article, and especially there's a table that does outline different criteria, and I think the point is: high index of suspicion and don't be rigid. Would you agree with that?

RC and WC: Yeah.

ES: This leads to a very related question: How do you decide when, so now, you have a high index of suspicion, you'd use your secondary test — how do you decide when, and who, and what patients — three part question.

WC: I think the patients — well, our goal here is to try to keep patients from progressing to where they have to go on a ventilator.

So, you know, the best outcome in this disease is if we can intervene with something that seems to be effective, eventually, that will keep patients from having to go into such severe respiratory failure where they have to go on a ventilator, because once we know that happens, for mortality is going to be quite high.

I think, again, the key is identifying them early and if they have a patient where these markers are elevated, suggestive of a cytokine storm and you see that their respiratory status is continuing to deteriorate over the first 24 to 48 hours that they're in the hospital, that's when you need to intervene.

You don't want to wait until they're on death's door, or you don't want to wait until they're having to go on a ventilator.

I think if we're going to intervene, and to be meaningfully helpful, we need to do it early.

RC: Yeah, I think that's clear. And the part of the problem is, you know, we don't know what's going to be best treatment for them. I'll just point out, this doesn't mean you can't treat the virus itself as well.

If we find out there's an antiviral therapy, great but still, you got to treat the cytokine storm if that's occurrent.

We don't have the answer at this point. We think we know what works for other side of kind of storms, or at least what have been reported to work for other cytokines storms and whether it will work for this particular viral infection, that is unknown.

And there are ongoing clinical trials, thank goodness, and hopefully we learn sooner than later from them, but it's very tough when the patient is in front of you and they're not enrolled at a clinical trial to realize they have a cytokine storm and do nothing.

So that's the rock and a hard place that we're currently in.

WC: Yeah. Hopefully, trials, unfortunately, they've had plenty of patients that are eligible for this type of intervention in terms of the trial criteria that were designed in Italy, but those trials have filled up and enrolled quite quickly, and we're hoping we'll get some outcome measures to look at various interventions, whether it's blocking interleukin-1 within anakinra, whether it's blocking IL-6 with tocilizumab, or sarilumab that targets the actual cytokine or whether targeting interferon gamma with empalumab are helpful intervention.

So we're hoping that we'll get some result or readouts from those within the next 4 to 6 weeks.

ES: So two final questions for you to sum up what you liked.

So you mentioned the three types of therapy, and you mention 4 to 6 weeks, but what would you do at the University of Alabama today or tomorrow?

Because, you're watching them and they're progressing, and they're not quite on the ventilator, are getting near there, and as you pointed out, this is when you want to intervene.

I'm just going to put you on the spot and you can refuse to answer if you want, because we all know it's speculative — I think we all know that this is best guess, and we know gamma is hard to get.

Anti-gamma is just a harder drug to get than blocking IL-1 or IL-6, which should more readily available.

Do you have any preferences or leave it up to a person's personal experience? Or any comments or do you want to decline?

RC: Yeah, it's tough.

I mean, part of it is, you know, a lot of these institutions, not certainly, not everybody, but a lot of institutions have ongoing clinical trials, and so you have to defer to those that are ongoing at the time, whether they're antiviral or not.

But for the patients who don't meet criteria for that, hopefully we can get them in another clinical trial. Dr. Chatham and I have a fair amount of experience with IL-1 blockade using recombinant human interleukin-1 receptor antagonist or anakinra, and so that would kind of be our bias.

But we don't know for this virus if IL-1 is going to be central, my guess is it probably will be. And there's other reasons specifically to like that agent, it's a recombinant human protein, so that's a good start. It's got a lot of safety data from its trials in RA, where it turned out not to be the greatest strike for rheumatoid arthritis, but we have a lot of pretty favorable safety data with that. It's got a short half-life of about 4 to 6 hours, and so even if it was causing harm, it's gone if you need to get it off. And it tends to work fast, and it's got a very big therapeutic window, including a lot of safety in that window. It's worked for even sepsis patients when you retrospectively, go back and look at sepsis trials and bring out the patients who have features of cytokine storm amongst those sepsis patients, it helped their survival.

So there's a lot of good reasons that that particular drug, if it turns out to work, would be something to consider.

WC: Yeah, I think most of the reported experience thus far in terms of whether these therapies are effective come out of China with their use of tocilizumab. I think that was chosen as the intervention when the Chinese physicians suspected that this was going on, because they noted that some of those patients had elevated IL-6 levels. Plus, I think that's the main intervention that they had access to.

I'm not sure there's access to IL-1 inhibitors in China. At least, there wasn't as of two years ago, the last time I was there and I'd spoken on this topic with them about just the cytokine storm syndrome in general.

So tocilizumab may be effective. Whether it's as effective and safe as IL-1 blockade, Hopefully some of these trials that are resulting out of Italy will let us know in the not too distant future.

ES: Thank you. I think we all agree that you should enter patients into trials because we have to know, and I think the point you made, whether it is pure antiviral, antiviral with or without a cytokine blockade, and we really don't know which one, I think that's an encouragement.

So on that note, is there any final messages you'd like to leave with our listeners?

RC: Just I'll just get my one, my one liner that I've been pushing for awhile, and that is: we have to treat not only the virus and we don't even know if we have effective therapy, hopefully we end up having something that proves useful, but we have to treat the patient's immune response to the virus if that's what's harming the patient.

WC: I would concur with that. I think the point of emphasis is, is to think about this early when these patients are admitted.

If there's an option to get them into a trial where we can answer some of these questions with these interventions, that's great, but if the patient doesn't have access to that option where you are, and the patient is clearly continuing to deteriorate with these markers, then I think offering this option whether it's with IL-1 blockade or IL-6 blockade is certainly something that should be strongly considered.

Because, again, we all want these patients to survive, but we also want them to survive with some meaningful quality of life, and once you've been on a ventilator for a week or two, even if you get off, that can be suspect.

The goal needs to get these patients stabilized, get their disease under better control, whether it's immunologic and/or virologic, and try to forestall them, having to go on mechanical ventilation.

ES: Thank you.

To me, I learned a lot and I hope our listeners did, and the take home message from my point of view, is early recognition, get on top of it, use the drug you're comfortable with, but, first of all, enter patients into a trial, because we have to get the answer, and hopefully, we will have an answer from Italy and directing it will be better.

So, on that note, I really want to thank you for the time, and I encourage everybody who listen to this to please read the article by Drs. Cron and Chatham as they expand upon these issues and do give a really nice table of different therapies.

And again, it is at jrheum.org.

Thank you and keep healthy.