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Fireside Chats: Top Abstracts Related to Still's Disease

Chapter 1: Randomized Double- Blind Placebo Controlled Study of Anakinra in Pediatric and Adult Patients with Still's Disease

Announcer:
Welcome to ReachMD. This Medical Industry Feature titled, Fireside Chats: Top Abstracts Related to Still's Disease, is sponsored by Novartis Medical Affairs.

Dr. Bella Mehta:
Just a brief introduction, I'm Bella Mehta. I'm a rheumatologist and assistant professor in medicine at the Cornell Hospital for Special Surgery. And Olga, do you want to introduce yourself?

Dr. Olga Petryna:
Hello, everyone. I'm Olga Petryna. I'm a rheumatologist and clinical assistant professor at NYU Langone Medical Center, Grossman School of Medicine.

Dr. Bella Mehta:
And let's get right into this. I'm going to talk about abstract 1633. This is being presented on Monday, but I think it's a very important abstract that we need to discuss. Again, it's very difficult to get randomized control trials in Still's disease, because it's a rare disease.

So, this is titled "A Randomized Double-Blind Placebo Controlled Study of Anakinra in Pediatric and Adult Patients with Still's Disease." So this is a multicenter study. The acronym they gave it is annaSTILLs. So Anakinra and Still's disease, and this is a 12-week study, and then they're enrolling patients with active in newly diagnosed Still's disease. And again, they include adult as well as pediatric patients. You know, in the abstract they say that they the goal was to enroll many more patients, but because of the slow recruitment, they stopped at 12. And they had 12 patients randomized into placebo and the treatment group, 6 in placebo, 6 in treatment group, and of the 6 who were in the treatment group 4 were assigned to 4mg/kg dose and 2 were assigned to 2mg/kg dose and again, there's a lot of pediatric patients with this. So, around 8 of them were kids and 4 were adults. They did use standard criteria, to recruit patients. So, ILAR criteria for under 16 and the standard Yamaguchi criteria greater than 16 years. And their primary objective was to see if these patients reached ACR30 with the absence of fever at week 2.

Again, pretty short duration, less likely because, anakinra is pretty fast-acting and you'd know if it's working quickly. Go to the next slide.

So here's one of the main results from the study. So on the left side, you can see these are patients who achieved an ACR30, 50, 70, or 90 response.

So in the treatment group they had 6 patients with anakinra and the placebo group had only 5 patients because 1 patient dropped out or was excluded because the patient actually had lymphoma and not Still's disease. So as you can see, pretty much a 100% of the treatment group reached ACR30, 50, and 70 and 5 of the 6 reached ACR90 this is at week 2. Importantly, no one in the placebo group reached any of these end points that they were looking at. They also mentioned in the abstract that eventually a lot of people in the placebo arm also dropped out because of various reasons; progression of the disease; some sort of side effect to the placebo. So again, it's difficult to do placebo-controlled studies in these sort of patients. So, they still have a good number. If you go on the right hand side, there are 6 patients that are in the treatment group and here you can see the blue dots showing the ACR90 responses. This is a pretty good and robust response to Still's disease.

So as you can see of the 6 patients, 4 of them start seeing an ACR90 response in the first week. 5 in the second week. And somehow, most of them continue in week 12. The patient number 1 here has, did not ever reach ACR90, but did reach ACR70 response. And

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again, in Still's disease, it is those patients who are responding to IL-1 blockade, you see them pretty early and that's what the studies sort of aiming to show. Again, a small study, but definitely important for Still's disease. We can go to the next one.

Chapter 2: Outcomes of an Evidence Based Guideline for the Treatment of Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Dr. Bella Mehta:
Olga, do you want to take this over?

Dr. Olga Petryna:
Of course. Yeah, so I think it's one of the very interesting studies presented this year. And it speaks about the outcomes of an evidence-based guideline implementations in the hospital system, when it came to the treatment of patients with suspected MAS and HLH. And I think why this abstract is important to begin with, because we all know that MAS or HLH is one of the most severe manifestations or complications of AOSD. and it has a mortality rate up to 20%.

And one of the contributing factors to why mortality happens is the delay in diagnosis and treatment. So if we can address this issue, obviously the outcomes would be much better and that's what the abstract speaks about. If you can move on to the next slide, it will give us an idea about this study in general.

So, what they did at the Boston Children's Hospital is they identify the patients with a high suspicion for HLH such as patients with an oncology or rheumatology note, fever, more than 38 Celsius, ferritin levels more than 500, and the patients who were seen either prior or post the implementation of the evidence-based guideline.

So first of all, what the guideline was, the guideline was that if there is a concern for HLH or MAS that would trigger a rheumatology consult. And then once the rheumatology consult was done, it was stratified patients on what needs to be done next. So if the patient had neuro symptoms that would trigger a neural consult, if patient had such a high suspicion for infection that would trigger ID workup.

A high suspicion for malignancy, that triggers malignancy workup. Once the diagnosis is confirmed, the guideline recommends the treatment regimen based on the severity of the disease, which looks like a very thought through approach to patients with these conditions. And then after this guideline was implemented, they follow up with patients before and after about criteria. And before the implementation was from January 18 to April 19 and post-implementation was from April 16 to, or rather prior pre-implementation, March 16 to April 18 and post-implementation generating to April 19th. So in this study, what they found that while after they started following the guidelines on diagnosis and treatment of patient with MAS, the mean time to diagnosis shortened more than by half. So the average time to diagnosis went from 8 and a half day to 2.8 days post-implementation. The hospital stay shortened by about 5 days or 4 days from 34 to 29.9 days. And the time from diagnosis to treatment shortened by half. So they went from average a week before patient could receive treatment to average of 3 days until patient received appropriate therapy.

What it resulted in is that the first-line treatment responder rate increased. So for pre-implementation the response rate was 30%, went up to 40%, which was reflected in a better outcomes and higher survival rate. So we see that prior to implementation of the guidelines, the survival rate was close to 75%.

It jumped up to 93.3% survival rate after they implemented the guidelines, which shows how useful it is in early diagnosing and treating patients with this condition to improve their outcomes. Also, when it comes to treatments that were used while the 3 treatments were most commonly used the IVIG, anakinra, and steroids, we see that there is a tremendous increase in use of IVIG in patients who were treated post-implementation of the guidelines.

So from 35%, they went up to 53% use of IVIG. And it was most important because use of IVIG was recommended in patients with suspected underlying infection. So that probably contributed to the, to the improved outcomes. So I think that that makes the study really important and we need more of such guideline implementation in the hospital systems for the patients who are at risk for MAS in Still's disease or any other autoinflammatory condition for that matter.

Dr. Bella Mehta:
True, I mean, especially given the high mortality…

Dr. Olga Petryna:
Correct.

Dr. Bella Mehta:
That these sort of patients come in, like if you can diagnose early start treating early, there's this direct mortality benefit.

Dr. Olga Petryna:

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Absolutely. I think we can go to the next one.

Chapter 3: Traditional Laboratory Parameters and New Biomarkers in Macrophage Activation Syndrome and Secondary Hemophagocytic Lymphohistiocytosis

Dr. Bella Mehta:
So I can talk about this one.

So again, this is an abstract presented today. And this is talking about similarly in MAS and secondary HLH the lab parameters and biomarkers in these 2 conditions. If you can go to the next slide?

So this is a study done from Italy and they have a lot of patients, around 82 patients, and they serially collected serum and biomarkers in these patients. And of course the traditional laboratory parameters that we usually measure in clinical care. So they had 38 patients who had secondary HLH 26 patients who had MAS in JIA patients, also 18 patients who did not have MAS, but JIA. And they measured biomarkers at T0, which is the time point, which is when they have active disease T1, which is 7 to 10 days from the start of therapy, and then T2, which is clinically inactive disease, usually 1 to 3 months from the disease onset. And they wanted to check how lab measures, which are traditionally used, changed and how interferon-related biomarkers have changed over time. So in the left side of this slide, you can see that typically, that biomarkers in the lab that we use the platelet count is decreased in MAS as well as secondary HLH whereas, the ferritin which is high in SJIA, but obviously increased dramatically in MAS and HLH. Some of the lab parameters that are part of the guidelines to diagnose these things AST which is elevated.

Something important to add on to the traditional lab markers is triglycerides and fibrinogen they give you a very good insight into if these patients are going into MAS or HLH. Again, these are life-threatening conditions, so you want to measure them early and in advance. So as you can see both in MAS and HLH triglycerides are elevated and so is fibrinogen decreasing.

So these are the lab parameters that we do know of. Some of the very interesting interferon-related biomarkers that actually you're hearing a lot in SJIA and Still's disease recently is neopterin. And what we see here is all of the interferon-related biomarkers, they measure your CXCL9, CXCL10, neopterin, and IL-18 is increased in MAS and HLH compared to SJIA. Also that CCX... Actually we can go to the next slide, they show these things much better. So here, the top part of this is a traditional ROC showing the biomarkers in MAS and the bottom half shows it in secondary HLH.

And what you can see is that CXCL9, neopterin, and IL-18, are elevated in these patients. Whereas in HLH CXCL9 and neopterin are not as much correlated with the IL-18 levels. If you can go to the next one.

So what we know is that what they saw is that neopterin levels do not correlate with flares, so the ROC curves were on T0, but the neopterin levels are staying elevated. CXCL9 does correlate with flares, so you can monitor it for flares.

Again, these are not typically available for nonresearch purposes, IL-18 yes, we can send it and it is used in MAS patients even, but it does take a little while to come back. So for clinicians, I think we still depend on the traditional lab measures and sometimes the IL-18 levels. Hopefully neopterin is much more widely available in the coming a few years and, there is a lot of clinical utility in using it.

Chapter 4: Risk Score of Macrophage Activation Syndrome (MAS) in Patients with Systemic Juvenile Idiopathic Arthritis (sJIA)

Dr. Olga Petryna:
All right. And this is another great abstract on the use of the score system to again, early diagnose MAS in patients with SJIA, which leads to the improved outcomes. So this particular study was designed to assess the laboratory markers that have highest probabilities course for development of MAS.

What they did, they selected – we can go to the next slide probably. They selected 69 patients with systemic JIA that did not have MAS at the time of enrollment. And they followed them over time where 41 did not develop MAS and 28 of the patients had at least one MAS episode. They followed them for the 10 years, for the 2-year follow-up and what they found and actually it reflects when the studies and publications were not published so far on the condition that second laboratory parameters like ferritin levels, LDH, AST, triglyceride levels, usually elevating patients who are experiencing symptoms suggestive of impending MAS. And then they use the regression coefficient-based scoring system to assign the weight to each of the laboratory parameter, put it in a scoring system, and saw how well the system predicts the MAS in patients that are at risk. So, you can see from the table on the right, that the scoring system had very high sensitivity and specificity in terms of predicting MAS and amongst the parameters used ferritin levels and LDH have the highest value with ferritin was score 3.5 and LDH having score of 2.5. As per this study, any patient with a score of 5 or more, had very high chance of developing MAS. So for example, 27 out of 28 patients whom developed a MAS had score of more than 5. And then patients who did not, from the 41 patients will not develop MAS only 8 patients had this score of 5.

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So it gives us a very good idea of what the alarming signs are. And then if you look at a table, if a patient had high ferritin LDH, that would be just enough to predict impending MAS. Also, AST and triglyceride, the like triglyceride levels had a fairly high predictive value and they were included in this scoring system.

So again, it emphasizes on importance of early diagnosis and treatment of MAS. And then now that we know more about the disease pathophysiology and the cytokine and laboratory profile. We can use those tools to predict who is the patient at risk and treat them better and more aggressively to improve their outcomes

So that will probably bring us to the next abstract that also is a very interesting study and innovative in a way.

Chapter 5: CCL2 and CCR2 in Adult Onset Still's Disease

Dr. Olga Petryna:
Studying CCL2 and CCR2 in adult-onset Still's patients. And you can go to the next slide here. So first we'll start with what CCL2 is. The chemokine C-ligand 2 and chemokine C-receptor 2, which are believed to be a chemokine that migrate monocytes and macrophages to the area of inflammation.

So theoretically, they are not specific. They could be seen in any inflammatory condition that presents with high innate immune system response that drives innate immune cells to the area of inflammation. What authors, they try to study the levels of CCL2 and CCR2 in patients with Still's disease, which is driven mostly predominantly by the innate immune system in rheumatoid arthritis, which is believed an autoimmune disease where the adaptive immune system is playing a more important role, but there is still a component of innate system involvement and in healthy controls, of course, that don't have any signs of the disease. What they did find is that levels of CCR2 were highly elevated in Still's patients as opposed to healthy controls or rheumatoid arthritis, which makes a lot of sense, theoretically. This is the conditions driven by the innate immune system.

And, unfortunately, did not really correlate well with the clinical manifestations, so clinical markers of disease activity in Still's. As well as it wasn't statistically significantly different between RA and Still's, mostly because a large gap between the individual presentation and symptomatology of the patients.

What was interesting though, when you look at the Still's patients, per se, the levels of the CCL2 were significantly higher in patients with active Still's. As opposed to patients with inactive Still's disease so that you see their bright blue and light blue bars on the left. And also what authors recognized is once the flare of Still's disease resolved, and patients went from active to remission, the levels of CCL2, CCR2 dropped.

So while it might not be a good diagnostic marker, might not differentiate Still's well from other conditions when it comes to reflect any inflammation or inflammatory response in AOSD patients between the active flare state and remission, that may be actually a quite useful tool. And that really just like another great abstract that summarizes how important it is to have tools to diagnose and treat Still's. So overall, I think all those abstracts, we just discussed, speak a lot about early diagnosis, effective, early treatment, and the tools that can be used for that. And as you see, while we still are having a huge unmet need with the diagnostic tools, it is getting better and we have more and more laboratory parameters we can use and more and more chemokines or cytokines we can measure.

And hopefully it will result in better diagnostic tools and of course improve our treatment approach.

Dr. Bella Mehta:
True. And I think I would add that not only diagnostic tools, but you know, calling the right specialty at the right time. I think sometimes rheumatologists are called in pretty late because you know, there's something else going on or they've not heard of this diagnosis. So just getting the ICUs and, getting some of the hospitalists, all of those people a little bit more attuned to what to look for and what to send out, simple things like fibrinogen, LDH. Those sorts of things also go a long way.

You know, the poster that you presented on implementing strategies to get them early diagnosis, I think that's the key. You know, these are patients who are sick, and you know, there's a high mortality, as you said.

Dr. Olga Petryna:
Yeah, I couldn't agree more with you. And as we see in that particular abstract on a guideline implementation, mortality rates improved significantly, hospitalization rates decreased and the hospital stay and outcomes improved so that reflects in better long-term outcomes and just like more effective way of treating patients.

Dr. Bella Mehta:
True. And, again, this is a rare disease, so this is not going to be always on people's minds. So you need to keep reiterating that to the colleagues saying this is something that needs referral, this is something that needs to be caught early.

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Dr. Olga Petryna:
I think it would be great whoever participated in this discussion, you can go ahead and scan the QR code and it will take you to a short survey about this group presentation.

All right. Thank you all for partaking. And enjoy the rest of the meeting.

Announcer:
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