STILL'S DISEASE: RESEARCH & CLINICAL TRIALS QUESTIONS & ANSWERS

Questions were answered by the panelists or representatives of the presenting organizations.

The names of those who asked questions have been removed, and some questions may have been edited to provide context or clarity.

Please consult your physician for any medical advice or guidance.

Diagnosis by exclusion was mentioned, it can be a pretty tedious process for the patient - are we getting any closer to faster means of diagnosis?

- Tiffany Westrich-Robertson (AiArthritis): There's no doubt it's tedious - and a bit frustrating. One reason it's a diagnosis by exclusion is simply because Still's is so complex and can mimic other, sometimes life-threatening, conditions. Infection is a good example. We hear many people with Still's claim the initial diagnosis was infection and were treated for that. Obviously if there is a rampant infection in your body, it needs to be treated (especially if there are high fevers involved). But you are right in that we need ways as the same time to at least consider, "Maybe this is Still's," *at the same time as being screened for infection*. That will come with more education, in time.

  Then there are those who do not have what is traditionally thought as 'classic' Still's - the triangle of high, spiking fever, salmon-colored rash, arthritis. Matter-in-fact, about 25% of people with Still's do not present with inflammatory arthritis at all at onset and many without chronic illness may never get the arthritic component. If our medical community is taught the "triangle", then what happens to the remaining patients who are having organ involvement as a first symptom? In those cases, and again, education will help, perhaps a check list of other features: "Is the patient also having episodes of high fevers that come and go, or rashes that fade quickly, or sore throat, swollen lymph nodes (etc)". If so, let's address the organ issues and also look at the bigger picture.

In regards to the question if we are closer, it depends on who you ask. Research is giving us some great information to help identify Still's - differentiate it - from other similar diseases (such as we saw in this webinar, compared to other diseases, like lupus or rheumatoid arthritis, IL-18 tends to be considerably higher in some Still's patients. These biomarkers can get us closer to diagnosing Still's, but given it's complex involvement of organs, and mirroring of serious infection and other potentially life-threatening conditions, some degree of 'exclusion' is likely to continue.

- Avalo: At this point in time, Still's Disease remains a diagnosis of exclusion

Is it true that Still's Disease at some point diverges in 2 directions? In a case of rheumatoid arthritis or a more systemic possibility?

- Tiffany Westrich-Robertson (AiArthritis): Still's is an autoinflammatory disease that stems from the innate side of the immune system - there are two sides, autoimmune diseases come from the adaptive side - or learned - and the innate side is not from something learned, but rather no known reason or cause. It's thought Still's can be triggered by infection or genetic mutation, but there's no one reason identified and, while it can be contributed in part to environmental factors, the adaptive side is more about the environmental triggers*.

  In saying this, it's not the Still's Disease specifically that branches into different directions (or comorbidities, additional diagnoses). It's the uncontrolled, underlying inflammation that redirects itself and attacks other parts of the body - at times, leading to additional diagnoses.

  **You can learn more about the two sides of the immune system here. The main thing to know about the adaptive immune system (where autoimmune diseases, like rheumatoid arthritis stem from), is that there needs to be a genetic PLUS environmental combustion of sorts. Smoking, gut or lung bacteria, or severe physical trauma are a few examples of something environmental, or external triggers. Environmental triggers can contribute to autoinflammatory disease onset, but it's still unknown how the innate side of the system was activated.*

Do you recommend asking your doctor to do genetic testing?

- Tiffany Westrich-Robertson (AiArthritis): There's no right or wrong answer here - and the answer will also depend in part on what your doctor believes, because they are the ones who would then be responsible for interpreting the results. As we talked about in this webinar, there are early biomarkers (like IL-18) that could indicate some differentiation between persons with Still's and those without Still's (which, in turn, could also help doctors choose treatments in the future that are more specific to individual biologic profiles). However, they aren't diagnostic. Furthermore, some biomarkers, like the Rheumatoid Factor (RF) or the HLA-B27 gene used in assessing spondyloarthritis, can be present in healthy individuals - so the question would be 'What is the benefit to getting one?' Here is a good article that discusses the pros, cons, and current climate of genetic testing in rheumatology.

STILL'S DISEASE: RESEARCH & CLINICAL TRIALS QUESTIONS & ANSWERS

Is it true that biologicals really accelerate remission?

- Rashmi Sinha (Systemic JIA Foundation): yes there is research showing that biologics do help increase chances of remission
- Tiffany Westrich-Robertson (AiArthritis): Additionally, there is research now that is showing those who start biologics earlier in their disease journey have a much higher chance of achieving remission - and drug free remission (where you no longer have to be on medications). Several studies were presented in 2020/2021 at both the EULAR and American College of Rheumatology annual scientific meetings. You can learn more about these by watching our debriefing videos here

Have you found a disconnect between doctors and their knowledge of the disease? Meaning a need to include more education of doctors while in training?

- Rashmi Sinha (Systemic JIA Foundation): Yes that would be great. If rheumatologists learnt more about Still's during training. But realistically speaking, I am not sure that will happen anytime soon.

Why is MAS prevalence higher in adult patients vs pediatric patients?

- Jeanette Bachir (SOBI): There is no data that could explain the difference in epidemiology data between adult and pediatrics.
- SOBI: As far as we are aware, there is currently no available data to explain the difference in epidemiology data between adult and pediatric patients. In addition, it is not clear that the occurrence is, in fact, different. The true incidence is unknown, particularly if one accepts the existence of "subclinical MAS" which would have an ill-defined boundary with MAS. A range of likelihoods between 10-15% is most often quoted for MAS in both sJIA and AOSD. See below e.g. a recent review:

  Tomaras S, Goetzke CC, Kallinich T, Feist E. Adult-Onset Still's Disease: Clinical Aspects and Therapeutic Approach. Journal of Clinical Medicine. 2021; 10(4):733. https://doi.org/10.3390/jcm10040733

Are there diagnostic criteria for sub-clinical MAS? How common is this?

- Rashmi Sinha (Systemic JIA Foundation): I am aware of proposed diagnostic criteria for subclinical MAS but not any published ones. Typically it's more based on labs
- Jeanette Bachir (SOBI): We are not aware of any, usually it is based on Lab investigation, while about 10% of patients with SJIA develop full-blown MAS, mild "subclinical" MAS may be seen in as many as one-third of patients with active systemic disease.

- SOBI: We are not aware of any diagnostic criteria for subclinical MAS. Usually, diagnosis is based on lab investigation, while about 10% of patients with SJIA develop full-blown MAS, mild “subclinical” MAS may be seen in as many as one-third of patients with active systemic disease. In addition the classification of “subclinical MAS” is not yet well defined, and is pretty much in the eye of the beholder. Virtually all published mention of the topic is based on a couple of articles from 2007-2008. One could picture a spectrum disorder which, in severe cases, fulfills the definition of (criteria for) MAS.

I was diagnosed with Still’s two years ago and probably had sJIA as a child which was active for about 9 years before I went into full remission. They’ve been checking my CRP and SAA levels monthly to check my disease activity. How effective are these checks compared to the complex lab test you talked about? And would they be good indicators as to when I could be trying to wean off biologics for example?

- Rashmi Sinha (Systemic JIA Foundation): Dr. Lachman is very good from what I know. If you have had Amyloidosis, then SAA is a good biomarker.I am not aware if biomarkers I mentioned (IL18, CXCL9 and S100a12) are elevated in SJIA with Amyloidosis. I can search around though and see if I find anything.

I have AOSD (diagnosed in 2006— at that time started on Kineret injections 100Mg s/c od) Presently taking Kineret 2x od. I need to know if this affects covid vaccine effectiveness— how much protection achieved with 2 shots of vaccine?

- Jeanette Bachir (SOBI): Based on the mechanism of action of Kineret, we do not expect that Kineret should affect the effectiveness of the vaccine. I also attach here a link on Eular viewpoints on this topic. They report that patients receiving anti rheumatic or immunosuppressive drugs can still be vaccinated; the only exception would still be the concomitant administration of ritux.
    - https://ard.bmj.com/content/80/4/411
- SOBI: Sobi does not have any data on file regarding any potential interactions between the available COVID-19 vaccines and Kineret. We also attach here a link on EULAR viewpoints on this topic. They report that patients receiving anti-rheumatic or immunosuppressive drugs can still be vaccinated with the exception of concomitant administration of rituximab. https://ard.bmj.com/content/80/4/411

Do we have any stats around adult SJIA patients and their risk of additional MAS events if they've only had it at onset?

- Jeanette Bachir (SOBI): I am afraid to say that we are not aware of any stats around this topic
- SOBI: We are not aware of any stats related to these events. From our understanding, there is currently no way to accurately predict who, after experiencing a first MAS event (~25% of MAS patients), will end up to have a subsequent episode (entering the ~5% with multiple events), but presumably the likelihood decreases over time.

STILL'S DISEASE: RESEARCH & CLINICAL TRIALS QUESTIONS & ANSWERS

In June 2020 I was diagnosed with Still and was close to an MAS. The triglyceride part was that it was pretty normal. Do you believe that the fact of having a healthy life and good nutrition may have prevented you from progressing to MAS?

- Jeanette Bachir (SOBI): As per the Eular approved criteria, MAS is diagnosed based on a combination of fever, high ferritin and additional two abnormal lab (PLT, fibrinogen AST or TG) so it could happen that PLT fib are abnormal and the rest is completely normal.
  Please be aware that the MAS diagnostic criteria require presence of fever, high ferritin plus two abnormal other lab tests. So it may be that the PLT and the fibrinogen are abnormal plus the others are normal. In addition, MAS is a result of hyperinflammation triggered by an underlying condition and we don't think that a good healthy life will prevent this complication.

- SOBI: The MAS diagnostic criteria require the presence of fever, high ferritin plus two abnormal other lab tests. It may be that the platelet and the fibrinogen are abnormal while the other tests results are normal. In addition, MAS is a result of hyperinflammation triggered by an underlying condition and there are no data to confirm that a good healthy life can prevent this complication

What is the longest someone has been on gamifant as a maintenance drug?

- Jeanette Bachir (SOBI): In the context of MAS, Gamifant is given to treat an acute disease (i.e. no maintenance therapy has been planned for MAS patients). Actually patients treated in our clinical trials have been receiving emapalumab for approximately 4 weeks.

- SOBI: In the context of MAS, emapalumab would be given to treat an acute disease (i.e. no maintenance therapy has been planned for MAS patients). Patients treated in our MAS clinical trial received emapalumab for approximately 4 weeks.

  In the context of primary HLH, one patient in the pivotal trial was on emapalumab for 245 days, and another for 232 days while waiting for HSCT. It should also be noted that emapalumab is not indicated as a maintenance medication for its approved indication in the US.

If in medicated remission, and CRP is stabilized, would you no longer be eligible for trial?

- Avalo: Patients in the Avalo Therapeutics (formerly Cerecor) AOSD Phase 1b trial are required to have active disease, which includes a recurring fever >38°C (or 100.4°F), within the last 5 days of the Screening and Baseline visits. There is also a washout period for biological DMARDs. Additional eligibility criteria can be found here.

Do you have any idea why some patients react so well to certain treatments and some don't?

STILL'S DISEASE: RESEARCH & CLINICAL TRIALS QUESTIONS & ANSWERS

- Tiffany Westrich-Robertson (AiArthritis): If we knew the answer to this then we'd all be on the best treatments and hopefully in remission. But, since we don't, here's my best educated response :). Still's Disease, and other autoinflammatory diseases (and autoimmune) are highly individualized per person. Take Still's specifically - not everyone has the traditional features, and even if they do those symptoms vary. You'll hear some patients say, "I never have the inflammatory arthritis, only lung issues and fever," while others will say, "The inflammatory arthritis is one of the worst parts." So, first part, we are all different.

  Then let's look at clinical trials, which we touched on in this webinar. As of today, clinical trials for the biologics we are prescribed have been tested in what is called the 'general patient population', or a group of people who have similarities that can be measured in large quantities, so in turn, research can scientifically demonstrate safety and efficacy. If the clinical trial had say 3 people in it and all 3 people did outstanding on the one drug, we know realistically there just needs to be 3 more people enrolled who may do poorly. It's a numbers game when it comes to trials and that's why those third phases require more people than phases 1 and 2. However, when these drugs then make it to market, the rest of us - those who wouldn't have met the inclusion criteria to be in the original trial, are prescribed the same treatment. But it worked for the people in the trial, the trial you may not have qualified to be in, and thus, you'll see a 40-60% success rate once we all get access. So, combine point one with this point, and well, you see why there is variety in how we respond.

  Our nonprofit is heavily invested in precision medicine, which involves pursuing trials and research that involve biomarkers, like IL-18, or that test subgroups who may be more likely to develop MAS. We know we are all different, we are all unique and as such we need to explore treatments and how they respond to smaller 'like' groups. This can be done in trials and also through what's called post-market surveillance, or following patients on a drug once to market and tracking why the drug is working for them or why it isn't. We have a long way to go, but we're getting there.

Is the study available for SJIA? / Is that trial open for kids or is just for adults?

- Barbara Sabatino (Avalo): The Avalo study is currently only in adults, as we are identifying the best dose, with the plan to move into a systemic JIA study if the results are positive from the adult study.
- Avalo: The Phase 1b study is currently only in adult Still's disease, as we need to identify the best dose and obtain additional safety data before moving into sJIA for those under 18 years of age.
- Jeanette Bachir (SOBI): I'm not sure which trial is being asking about , if this is the SOBI trial : Yes the SOBI trial iis open for adult and pediatric patients.
- SOBI: We are not sure which trial Pauline is asking about (the Sobi trial or Avalo Therapeutics trial). The SOBI trial NCT05001737 will be open for adult and pediatric patients.

STILL'S DISEASE: RESEARCH & CLINICAL TRIALS QUESTIONS & ANSWERS

My daughter's IL-18 has reached 400,000. She is now on Gamifant for 8 months now and has brought it to 10-14,000. Could she qualify in the near future with her age (7yrs old)

- Avalo:The Avalo study is currently only in adults with Still's Disease. The Phase 1b study is currently only in adults in order to identify the best dose and obtain additional safety data before moving into sJIA for those under 18 years of age.

"Refractory" means not controlled with NSAIDs and steroids? Do I understand that correctly?

- Tiffany Westrich-Robertson (AiArthritis): It's not limited to just NSAIDs and steroids, it's treatments in general - more often biologics or stronger drugs than NSAIDs and steroids. Often we will hear patients say, "I've tried every biologic there is and nothing is working!" That's an example of a person being resistant, or difficult to treat, with the drugs that exist on the market today.

When can your drug that inhibits IL18 be on the market?

- Avalo: Avalo is working hard to enroll and complete the current clinical trial in Adult Onset Still's Disease. The data produced will help us plan further clinical development programs and engage with regulatory agencies about next steps.

What age is considered Still's disease rather than SJIA, I know they are the same disease but different stages of onset.

- Tiffany Westrich-Robertson (AiArthritis): SJIA is onset under 16 years of age and adult-onset is considered onset at 16 years of age or after. In saying this, since some patients go a long time undiagnosed, it is possible a person who had onset prior to the age of 16, but diagnosed later in life, may receive the AOSD diagnosis. The good news is it's now considered a continuum "Still's Disease" and this should help at least with treatments.
- SOBI: The ILAR (International League of Associations for Rheumatology) defines sJIA as occurring before the age of 16. Below is a link providing the ILAR classification criteria

  ILAR Classification Criteria for Juvenile Idiopathic Arthritis (JIA) – MedicalCRITERIA.com

STILL'S DISEASE: RESEARCH & CLINICAL TRIALS QUESTIONS & ANSWERS

I've recently been asked by my Rheumatologist if I'd be open to taking 2 Biologics. Is that something that people with AOSD and other Autoimmune/Autoinflammatory conditions can do?

- Tiffany Westrich-Robertson (AiArthritis): The goal for treating your Still's Disease, and other similar diseases, is to get the inflammatory activity under control. Sometimes this involves multiple treatments, like biologics and steroids or DMARDS (like methotrexate), for example. At times, the rheumatologist may feel your disease is complex (perhaps it's not responding well to existing treatments, called 'refractory', or you may have comorbidities that complicate it. Or it may be that you have some features that mimic similar diseases (or overlap with them) - like spondyloarthritis, for example, where research has shown patients with that condition respond well on a specific drug. In these cases, it is not uncommon for a doctor to suggest consideration of blended treatments, with the goal to get your disease controlled. However, with added treatments come potential side effects that need to be discussed with your doctor (and possibly family members/significant other). Then, together, you can make an informed decision.

How do you recommend talking to your primary care physician given it's such a rare disease?

- Tiffany Westrich-Robertson (AiArthritis): To start, I'm going to put primary care physicians (PCP) in the same category as hospital workers, nurses, and specialists unfamiliar with Still's Disease - because the approach would probably be similar - regardless of the type of professional. What I don't recommend is saying something like, "So, I have Still's Disease, do you know anything about it?" but still asking a question to gage their knowledge and WHY you would like to know their existing level:

  "My main health challenge (or one of them, if applicable) is that I live with Still's Disease. As it's a rare disease, and not a lot of information about it is shared among health professionals, I was wondering how familiar you are with it?" Let them answer… this approach you are simply assessing education levels without insulting their professional experience or expertise.

  Then, depending on their answer, you should tell them why … Why is this important to you? Example: "I was asking because it's such a huge part of my life, including how I manage my everyday healthcare and wellness. I don't expect anyone to really know much about it, because I don't think it comes up much in medical practice, but it's important to me that you - as my (PCP) can become familiar with it.

  Listen to what they say. If they are the doctor for you, they will care that this is important to you. If they disregard your concern, that's a red flag to seek out a different doctor (if possible). Assuming they would be open to learning more - no matter what their level of knowledge is - you can send them to our website for awareness materials and our disease brochures (which they may want for their office, too?) These can be found at www.aiarthritis.org/stillsdisease

The research shown where IL-18 was good for COPD patients seemed promising. But how does COPD and Still's Disease relate to one another?

- Avalo: Chronic obstructive pulmonary disease (COPD) is characterized by chronic lung inflammation. IL-18 has been shown to play a critical role in various inflammatory diseases.

Your slide said the first data would be ready this year (Fall I think)? So how many people do you need in your trial right now to meet that deadline? Where does a person need to live to participate?

- Avalo: The estimated enrollment in the study is 12 participants. There are currently several study sites in the United States, Belgium and Ukraine. In California, there are two sites recruiting: TriWest Research Associates in El Cajon and Biosolutions Clinical Research Center in La Mesa. In Florida, there is one site at the University in Gainesville. There is one site in Maryland: Arthritis Care Specialist in Columbia. There is one site in Michigan at the University of Michigan in Ann Arbor. Please speak with your physician. More information about the study can be found here.