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<https://reachmd.com/programs/insights-il-17-targeted-psa-therapies/the-role-of-il-17-in-psa-pathophysiology-and-treatment-plans/11127/>

Released: 12/23/2019

Valid until: 12/23/2020

Time needed to complete: 15 Minutes

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The Role of IL-17 in PsA Pathophysiology and Treatment Plans

Announcer:

Welcome to CME on ReachMD. This activity, entitled "The Role of IL-17 in PsA Pathophysiology and Treatment Plans" is provided by National Psoriasis Foundation with educational partner Rockpointe and is supported by an independent educational grant from Lily.

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Dr. Caudle:

Psoriatic arthritis is a complex disease with multiple immune cells and signaling molecules playing critical roles in its progression. That's why today we'll be investigating these immune-mediated inflammatory pathways, particularly those involving IL-17 and how they inform the latest guidelines in disease management. This is CME on ReachMD, and I'm your host, Dr. Jennifer Caudle. And joining me to discuss the rationale for newer therapies for psoriatic arthritis is Dr. Siba Raychaudhuri. Dr. Raychaudhuri, welcome to the program.

Dr. Raychaudhuri:

Thank you. Thank you very much.

Dr. Caudle:

To start us off, Dr. Raychaudhuri, can you give us an overall picture of the pathophysiology of psoriatic arthritis and how these molecular changes, when unchecked, lead to disease progression?

Dr. Raychaudhuri:

In psoriatic arthritis and also in psoriasis a polymorphism of a number of genes have been observed such as HLA, HLA-B27, IL23 receptor, and IL12B. Polymorphism can be influenced by various environmental factors, such as infections, toxins, with medications such as with lithium or anti-malarial agents, and biomechanism forces. These factors can induce an immune-mediated inflammation and that leads to the pathology typical for psoriasis and psoriatic arthritis, such as psoriasis plaque, synovial inflammation, synovitis, enthesitis, bone erosion, and new bone formation. Let me also tell briefly about the immunopathologic mechanisms responsible in psoriatic disease. Pathologic memory T cells migrate to the disease site and then interact with the antigen-presenting cells, which may cause liberation of area of cytokines. But T-cell interacts with the addition molecule into the cells and goes into the interstitium, and there the T-cell interacts with the antigen-presenting cells. Most important molecular interaction is between MHC of the APC. APC is the antigen-presenting cell, with the T-cell receptor and the costimulatory molecules such as CD20 and CD26, and CD124 and CD40. These molecular interactions between the antigen-presenting cells and T-cells generate area of cytokines, including IL17. And these cytokines can induce immune-mediated inflammation responsible for psoriatic arthritis. There are various T-cell subpopulations. The antigen-presenting cell and the T-cell interact under the influence of certain cytokines differentiate to the number of subpopulation which has specific cytokine signatures, such for Th1 cells interferon gamma, and for Th2, it is IL4, and for Th17, the signature cytokines are IL17A, IL17F, and IL22, whereas for Tregs, it is TGF beta and IL10. For Th17 cells, various cytokines help in differentiating the cells, which are TGF beta, IL6, and IL23. And there is important transcription factors, and signaling proteins such as STAT3 and RORgammaT which will help to differentiate the naive cells to Th17 cells. All of the aforementioned molecules could be a target for treatment of psoriatic arthritis.

Dr. Caudle:

That's great, Dr. Raychaudhuri. And if we focus on the role of IL17 in the pathogenesis of psoriasis, psoriatic arthritis, and associated spondyloarthritic diseases, what can you tell us about that?

Dr. Raychaudhuri:

Both skin and synovial tissue of psoriatic arthritis is enriched with IL17-positive T-cells. IL17-producing T-cells are enriched in the synovium of psoriatic arthritis, and the same thing can be seen in psoriasis plaque. Various external and internal triggering factors such as gut microbiome HLA genetic background and biochemical traits will trigger secretion of cytokines like IL23, TGF beta, IL6, and IL1B. And that will influence to differentiate naïve T-cells to Th17 cells, and then these Th17 cells make critical cytokines like IL22 and IL17. They do make TNF alpha also. And then IL17 and TNF alpha induce the inflammatory component of the disease. Like synovial inflammation, block formation that is psoriasis, and bone erosion.

Dr. Caudle:

For those of you who are just joining us, this is CME on ReachMD. I'm your host, Dr. Jennifer Caudle, and I'm speaking with Dr. Siba Raychaudhuri about the rationale for newer psoriatic arthritis therapies. So, Dr. Raychaudhuri, returning to our discussion on treating psoriatic arthritis, what do the current GRAPPA guidelines recommend for the use of IL17 inhibitors?

Dr. Raychaudhuri:

GRAPPA guidelines is based on the six clinical domains of psoriatic arthritis, which are peripheral arthritis, axial disease, enthesitis, dactylitis, skin involvement, and nail psoriasis. According to GRAPPA treatment schema, anti-IL17 can be considered for all these domains. More so for axial disease, enthesitis, and nail involvement even before considering traditional DMARDs such as methotrexate.

Dr. Caudle:

Another set of guidelines come from the American College of Rheumatology and the National Psoriasis Foundation. So, how have those guidelines addressed the use of IL17 inhibitors in the treatment of patients with psoriatic arthritis?

Dr. Raychaudhuri:

American College of Rheumatology, that is ACR, and NPF guidelines for psoriatic arthritis recommend for treatment of naïve or untreated patients with active psoriatic arthritis the use of TNF inhibitor biologic or oral small molecule is recommended over an interleukin IL17 inhibitor. But an IL17 inhibitor biologic, when used instead of TNF inhibitor biologics in patients with severe psoriasis are contraindications to TNF inhibitor biologics. And may be used instead of oral small molecules in patients with severe psoriasis or severe psoriatic arthritis. In patients with active psoriatic arthritis, despite treatment with oral small molecules, switching to a TNF inhibitor and/or an IL17 inhibitor or an IL12, IL23 inhibitor biologic is recommended over switching to a different oral small molecule.

Dr. Caudle:

And what about the EULAR guidelines with respect to the IL17 inhibitors; how are they different?

Dr. Raychaudhuri:

EULAR recommendations for management of psoriatic arthritis is based on Phase 1 through Phase 4. In Phase 1, clinical diagnosis of active psoriatic arthritis is established. General methods such as NSAIDs and joint glucocorticoid injection can be considered. If disease progresses, that is in phase 2, then EULAR recommends to try methotrexate and other DMARDs. If it still remains active, that is in phase 3, biologics including anti-IL17 have been recommended by EULAR.

Dr. Caudle:

Now that we know more about what the latest guidelines recommend, Dr. Raychaudhuri, can you give us a brief review of some of the safety and efficacy data for the available IL17 inhibitors, secukinumab and ixekizumab?

Dr. Raychaudhuri:

The randomized, double-blind FUTURE-5 trials for secukinumab have demonstrated the efficacy of secukinumab on joints of psoriatic arthritis compared to the placebo in anti-TNF naïve and anti-TNF resistant or anti-TNF failure patients. The ACR responses; ACR20, ACR50, and ACR70 were actually quickly, within 12 weeks, and they were maintained over time. Overall, secukinumab was found to be effective, safe, and also the efficacy continued for 24 weeks. Follow-up studies demonstrated that this efficacy can last for two years. Secukinumab 300 mg resulted in better outcomes in terms of resolution of enthesitis and dactylitis versus secukinumab 150 mg and placebo. Secukinumab 150 mg also performed better than placebo. In respect to ixekizumab, in the SPIRIT-P1 trial for ixekizumab, ACR and PASI responses were achieved quickly within eight weeks, and its efficacy could be maintained over time. With ACR20 response, efficacy was around 60%, which is comparable to other drugs, including anti-TNF and secukinumab. Similar results were seen in ACR50 response. With respect to skin, PASI-75 response was more than 80%. And generally we see PASI-75 a little less with

anti-TNF, and that is around 60% to 70%. The PASI-75 response of anti-IL17 antibody for psoriasis has been found to be significantly more compared to anti-TNF in all available anti-IL17 antibodies. For ixekizumab in the SPIRIT-P1 and P2 trials, with ixekizumab every two weeks and every four weeks was associated with a significantly greater number of patients reporting no dactylitis and no enthesitis at week 24 versus placebo.

Dr. Caudle:

And before we close, Dr. Raychaudhuri, what are the main takeaways you'd like to leave with our audience?

Dr. Raychaudhuri:

IL17 is a key player in the pathogenesis of psoriasis and psoriatic arthritis. Targeting IL17 with the newer pharmacotherapy is an effective means of mitigating disease-activating and improving outcomes in patients with psoriatic arthritis.

Dr. Caudle:

Well, you've certainly given us a lot to think about Dr. Raychaudhuri, and it's great knowing that improved outcomes are possible thanks to these newer advances. But unfortunately, that's all the time that we have for today, so I'd like to thank my guest, Dr. Siba Raychaudhuri for helping us better understand the role of IL17 in the pathophysiology of psoriatic arthritis, as well as the recommendations for IL17 therapies in our treatment plans. Dr. Raychaudhuri, it was wonderful speaking with you today.

Dr. Raychaudhuri:

It has been my pleasure to talk with you. And thank you for arranging this radio talk.

Announcer:

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