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Understanding Dual Inhibition of IL-17

ReachMD Announcer:
Welcome to ReachMD. This medical industry feature is titled “Understanding the Dual Inhibition of IL-17A + IL-17F,” is sponsored by UCB. Here are your hosts Dr. Bret Sohn and Dr. Eric Anderson.

Dr. Sohn:
Hey everybody! Welcome to BIMZELX & Cold Brew, where we dive into the science behind immune-mediated inflammatory diseases with coffee in hand. Cheers bud.

Dr. Anderson:
Cheers.

Dr. Sohn:
I'm Dr. Brett Sohn, a rheumatologist based in Stamford, Connecticut. I specialize in all aspects of rheumatology, and I'm excited to talk about the science of BIMZELX today.

Dr. Anderson:
And I'm Dr. Eric Anderson, also a rheumatologist currently based in Oconomowoc, Wisconsin. Looking forward to chatting through the importance of dual inhibition and why it might inform the way we think about inflammation in practice.

Dr. Sohn:
Today, we're focusing on the mechanism of action of BIMZELX, the first and only approved dual inhibitor of IL-17A and IL-17F.

BIMZELX is currently approved for use in adults with the active psoriatic arthritis, active non-radiographic axial spondyloarthritis with objective signs of inflammation, active ankylosing spondylitis, moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy, and moderate-to-severe hidradenitis suppurativa.

Dr. Anderson:
We have pulled in questions from doctors throughout.

Dr. Sohn, want to kick us off?

Dr. Sohn:
So let’s get into it! How IL-17F fits into the picture, why dual inhibition matters, and how understanding the MOA may help us make informed treatment decisions.

Dr. Anderson:
First, let's take a look at how the immune system plays a role in the inflammation cascade. What is the IL-17 cytokine family, and what role does it play in chronic inflammation?

Dr. Sohn:
Important place to start. The IL-17 family of cytokines consists of 6 isoforms with roles across proinflammatory signaling and immune responses. Two members of the family, IL-17A and IL-17F, play significant roles in many rheumatic diseases, including AS, nr-axSpA, and PsA. These two cytokines share 55% homology and have overlapping roles.

Dr. Anderson:
Breaking it down, we see both IL-17A and IL-17F are produced by two parts of the immune system: the adaptive immune system and the innate immune system. That means IL-17 isn't coming from just one source, it's being produced by both arms of the immune response.

The IL-23-dependent adaptive immune pathway produces TH17 cells, which generate both IL-17A and IL-17F, and play a major role in driving inflammation.

However, they aren't the only source of these cytokines.

The IL-23-independent, innate immune system pathway, which includes cells like the mucosal-associated invariable T cells, gamma-delta T cells, and ILC3s also produces IL-17A and IL-17F.

Dr. Sohn:
Dr. Anderson, what you bring up is really important. While the adaptive immune response needs IL-23 to produce IL-17A and IL-17F, the innate immune response does not. It works independently of IL-23.

What's more, innate immune cells tend to make more IL-17F than IL-17A, so even if you block IL-23, IL-17A and IL-17F can still be produced by the innate immune system. Therefore, inhibiting the IL-23-dependent pathway may not fully suppress IL-17A and IL-17F production and proinflammatory signaling.

Dr. Anderson:
And IL-17A and IL-17F have similar downstream effects.

Dr. Sohn:
IL-17A and IL-17F trigger the production of proinflammatory mediators, like cytokines, chemokines, and tissue-remodeling matrix metalloproteinases, all fueling chronic inflammation.

Dr. Anderson:
We have seen in preclinical studies that IL-17A has higher potency compared to IL-17F, but IL-17F is far more abundant, up to about 30 times higher than IL-17A in inflamed PsA and AS tissue. IL-17F is overexpressed in skin and synovial tissues and highly elevated in serum across PsA, AS, and psoriasis.

Dr. Sohn:
Exactly. In addition, it has been observed in in vitro studies that there's a difference when IL-17A and IL-17F peak in inflammation. For example, it's been observed that IL-17F ramps up over time and may become more prominent in chronic inflammation.

Dr. Anderson:
So, now we know there are some differences between IL-17A and IL-17F. Do we know whether dual inhibition makes a difference in inflammation?

Dr. Sohn:
Preclinical in vitro studies have shown that inhibiting both IL-17A and IL-17F provides more suppression of inflammation than inhibiting either cytokine alone.

Looks like we've got a question!

Dr. Anderson:
@DrCarmenRheum asks, “Is it really that important to inhibit both IL-17A and IL-17F?”

Great question. While IL-17A has greater potency, IL-17F is more highly elevated in the psoriatic skin and serum of patients with PsA, nr-axSpA, and AS.

Dr. Sohn:
And here's where it gets interesting. IL-17A and IL-17F don't just signal separately, they form homodimers A/A and F/F, and heterodimers A/F. All three dimers signal through the IL-17RA/RC complex that leads to downstream inflammation.

Dr. Anderson:
IL-17A inhibitors bind to and inhibit the activity of the IL-17A/A and IL-17A/F dimers. However, they do not bind to the IL-17F/F dimer, which leaves it free to bind to the IL-17 RA/RC receptor. Therefore, targeting IL-17A alone only partially interferes with the IL-17 inflammation pathway.

Dr. Sohn:
Exactly.

Dr. Anderson:
Now that we've had an immunology refresher, let's talk about how BIMZELX works.

Dr. Sohn:
BIMZELX works differently than current IL-17 inhibitors. It's a monoclonal antibody designed to block both IL-17A and IL-17F, including their homo- and heterodimeric forms, which are produced by both adaptive and innate immune pathways.

Dr. Anderson:
By selectively targeting IL-17A and IL-17F, BIMZELX binds to all three dimers, A/A, A/F, and F/F regardless of if they come from the adaptive or innate immune pathway.

And then, by targeting IL-17A and IL-17F dimers, BIMZELX helps interrupt the receptor activation that drives chronic inflammation.

Let's take some time to answer another question. @DrBerdy62 wants to know, "Is BIMZELX a bispecific antibody?"

Dr. Sohn:
No, BIMZELX is not a bispecific antibody. It is a dual specific. As we mentioned, it is a single monoclonal antibody with two identical arms, and each arm can bind to either IL-17A or IL-17F homodimers or the IL-17A/F heterodimer.

BIMZELX selectively targets a region of IL-17A and IL-17F common to both cytokines. This is important because it allows both IL-17A and IL-17F to be neutralized, no matter their relative abundance, which we know can vary from one disease state to another.

Dr. Anderson:
Let's take our next question. @RheumWatch1 asks, "How is this different from other IL-17 inhibitor treatments?"

So, current IL-17A inhibitors block the A/A homodimer and the A/F heterodimer. This can leave the F/F homodimer with the potential to drive inflammation. As I mentioned earlier, BIMZELX is designed to inhibit all three dimers, A/A, A/F, and F/F. We're not saying it guarantees results, but mechanistically, it offers more suppression of the IL-17 inflammatory pathway.

Dr. Sohn:
@Kim_MD has an important question. "How do you explain it to your patients what makes BIMZELX different?"

I tell them that BIMZELX works differently by blocking not just one, but two critical drivers of inflammation: IL-17A and IL-17F.

Dr. Anderson:
Let's talk about what dual inhibition might mean in practice.

Dr. Sohn:
So @DrJen_MD has a question, and she says, "How does understanding the MOA of dual inhibition inform your treatment decisions in practice?"

So, the mechanism of action doesn't dictate outcomes, and the clinical relevance of the MOA is unknown. We've had IL-17A inhibitors available for a while now, but this is a different type of IL-17 inhibitor by targeting two cytokines.

Dr. Anderson:
And the more we understand the mechanism of disease and newer inflammatory targets like IL-17F, the better we can explain it to patients and make confident, thoughtful decisions.

This has been such a great discussion and we've covered a lot around IL-17 dual inhibition of IL-17A + F.

Dr. Sohn:
For me, it comes back to precision. Understanding how A and F work together gives us more confidence in how we approach treatment.

BIMZELX is the first and only approved therapy to target both IL-17A and IL-17F, offering a different approach to IL-17 pathway inhibition, and adds a different treatment option to the landscape.

BIMZELX is currently approved in rheumatology for use in adults with active psoriatic arthritis, active non-radiographic axial spondyloarthritis with objective signs of inflammation, active ankylosing spondylitis, moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy, and moderate-to-severe hidradenitis suppurativa.

Dr. Anderson:

We always encourage colleagues to dig into the data, talk to patients, and think critically about how to evolve our approach.

Dr. Sohn:
That wraps up today's conversation. Thanks for tuning in.

Dr. Anderson:
And please stay tuned for the Important Safety Information for BIMZELX and see full Prescribing Information. And look out for the next video in the BIMZELX & Cold Brew series.

Announcer:
INDICATIONS
BIMZELX (bimekizumab-bkzx) is indicated for the treatment of adults with active psoriatic arthritis, active non-radiographic axial spondyloarthritis with objective signs of inflammation, active ankylosing spondylitis, moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy, and moderate-to-severe hidradenitis suppurativa.

IMPORTANT SAFETY INFORMATION

Suicidal Ideation and Behavior
BIMZELX may increase the risk of suicidal ideation and behavior (SI/B). A causal association between treatment with BIMZELX and increased risk of SI/B has not been definitively established. Prescribers should weigh the potential risks and benefits before using BIMZELX in patients with a history of severe depression or SI/B. Advise monitoring for the emergence or worsening of depression, suicidal ideation, or other mood changes. If such changes occur, instruct to promptly seek medical attention, refer to a mental health professional as appropriate, and re-evaluate the risks and benefits of continuing treatment.

Infections
BIMZELX may increase the risk of infections, including serious infections. Do not initiate treatment with BIMZELX in patients with any clinically important active infection until the infection resolves or is adequately treated. In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing BIMZELX. Instruct patients to seek medical advice if signs or symptoms suggestive of clinically important infection occur. If a patient develops such an infection or is not responding to standard therapy, monitor the patient closely and do not administer BIMZELX until the infection resolves.

Tuberculosis
Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with BIMZELX. Avoid the use of BIMZELX in patients with active TB infection. Initiate treatment of latent TB prior to administering BIMZELX. Consider anti-TB therapy prior to initiation of BIMZELX in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Closely monitor patients for signs and symptoms of active TB during and after treatment.

Liver Biochemical Abnormalities
Elevated serum transaminases were reported in clinical trials with BIMZELX. Test liver enzymes, alkaline phosphatase, and bilirubin at baseline, periodically during treatment with BIMZELX, and according to routine patient management. If treatment-related increases in liver enzymes occur and drug-induced liver injury is suspected, interrupt BIMZELX until a diagnosis of liver injury is excluded. Permanently discontinue use of BIMZELX in patients with causally associated combined elevations of transaminases and bilirubin. Avoid use of BIMZELX in patients with acute liver disease or cirrhosis.

Inflammatory Bowel Disease
Cases of inflammatory bowel disease (IBD) have been reported in patients treated with IL-17 inhibitors, including BIMZELX. Avoid use of BIMZELX in patients with active IBD. During BIMZELX treatment, monitor patients for signs and symptoms of IBD and discontinue treatment if new onset or worsening of signs and symptoms occurs.

Immunizations
Prior to initiating therapy with BIMZELX, complete all age-appropriate vaccinations according to current immunization guidelines. Avoid the use of live vaccines in patients treated with BIMZELX.

MOST COMMON ADVERSE REACTIONS

Most common (≥1%) adverse reactions in plaque psoriasis and hidradenitis suppurativa include upper respiratory tract infections, oral candidiasis, headache, injection site reactions, tinea infections, gastroenteritis, herpes simplex infections, acne, folliculitis, other candida infections, and fatigue.

Most common (≥2%) adverse reactions in psoriatic arthritis include upper respiratory tract infections, oral candidiasis, headache,

diarrhea, and urinary tract infections.

Most common (≥2%) adverse reactions in non-radiographic axial spondyloarthritis include upper respiratory tract infections, oral candidiasis, headache, diarrhea, cough, fatigue, musculoskeletal pain, myalgia, tonsillitis, transaminase increase, and urinary tract infections.

Most common (≥2%) adverse reactions in ankylosing spondylitis include upper respiratory tract infections, oral candidiasis, headache, diarrhea, injection site pain, rash, and vulvovaginal mycotic infection.

Please see the full Prescribing Information at BIMZELXhcp.com.

ReachMD Announcer:
If you missed any part of this discussion or to find other programs in this series, visit ReachMD.com/industryfeature. This is ReachMD. Be part of the knowledge.

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