Pharma Intelligence
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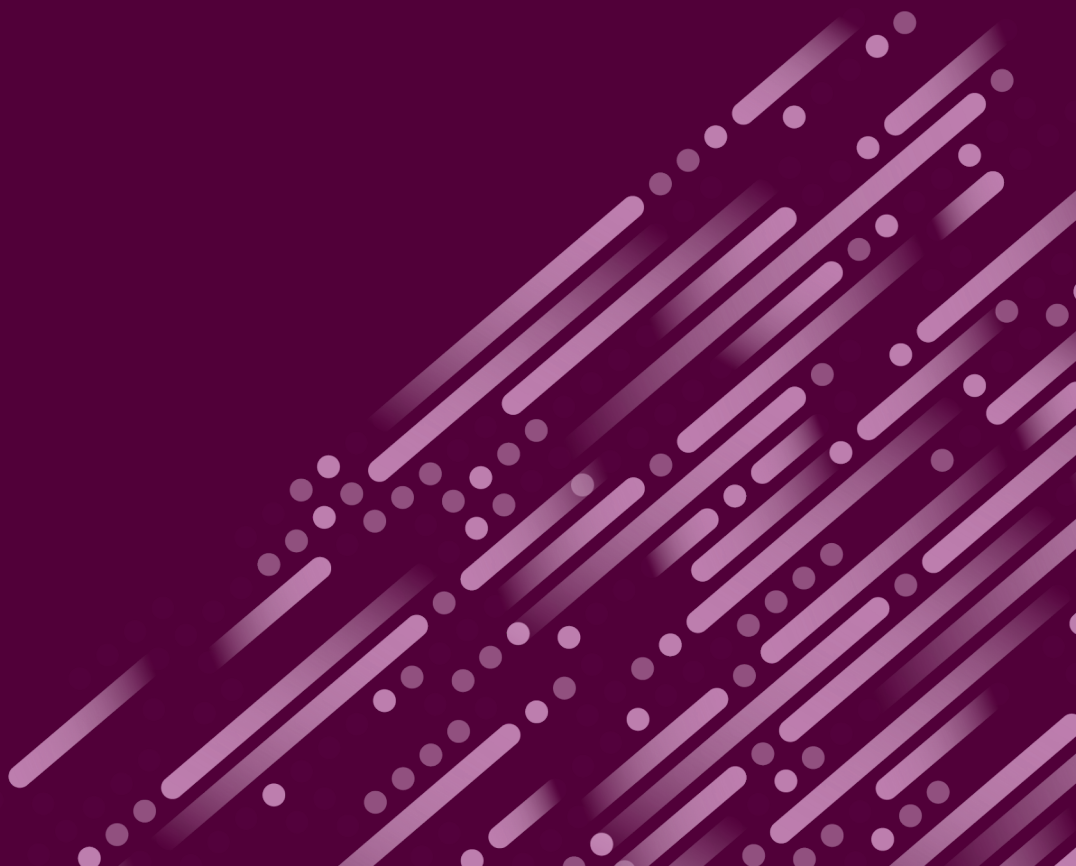
The 2021 American Academy of Dermatology (AAD) Conference



2021 AAD Conference

Day 3 Update - Sunday April 25, 2021

On Sunday the AAD VMX meeting began winding down but several educational medical sessions took place including one on Janus kinase (JAK) inhibitors in the context of dermatology as well as one highlighting the implications of climate change on dermatology. Technical issues remained with posters still unavailable on the AAD VMX platform.

Select highlights from our team of analysts are below:

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S003 JAK Inhibitors: Live Question and Answer Session

One topic dominating the spotlight at the 2021 AAD VMX was the promise of JAK inhibitors. Despite safety concerns and black box warnings with the class, presenting dermatologists seem overwhelmingly excited about this class and are quick to differentiate the origin of the black box warnings as being sourced from the distinctly different, higher-risk population of arthritis patients, and these risks may not necessarily relate to dermatological patients. Dermatologists expect to have the option for flexible dosing with JAK inhibitors, to help mitigate the risks that were most often seen with the higher dose and presenters see potential for JAK inhibitors to be used across several indications. There were not specific diseases called out where specific JAK inhibitors might be more effective, and no predictive biomarkers currently point to a personalized approach to treatment either by a specific JAK inhibitor or the class in general.

Presenters spoke to the fact that JAK inhibitors should not be viewed solely as broad immunosuppressants, like prednisone, mycophenolate, methotrexate, or cyclosporin, and that they may sit in a sweet spot between those broad

immunosuppressants and the more targeted biologics, for diseases affected by more than just one or two cytokines. On the subject of JAK inhibitor use in vitiligo, a presenter commented on how they use a steroid, calcineurin, and phototherapy as first line treatment, but if a patient is not responding or if they are unable to do phototherapy, they will quickly offer a JAK inhibitor either topically or orally. Topical JAK use is only currently available via compounding, but they are looking forward to ruxolitinib cream becoming available in eczema and are currently asking their vitiligo patients if they have comorbid eczema in preparation for that approval. They noted that even if as much as 20% BSA is affected by the disease, they will still go to a topical compounded JAK, but the limitation rests on the patient's resources as they would need to buy several tubes for such a large area. However, the presenter did note that with more than 10% BSA or unstable active disease, where it is hard to keep chasing down depigmented areas with cream, they would recommend oral agents.

A pediatric dermatologist noted that approval of tofacitinib approval in JIA down to age 2 has increased her comfort in using this drug in pediatric conditions, like alopecia areata.

On the topic of combining JAK inhibitors with other therapies, one physician spo e about his positive e perience in using tofacitinib on top of dupilumab as a sort of rescue therapy for severe atopic dermatitis and how this may replace methotre ate or cyclosporin in that capacity. In terms of adding a JAK inhibitor to broad immunosuppressants, physicians would be more careful, but there may still be a place for such a combination in patients with very severe disease. As for rates of relapse with JAK inhibition, it seems that they will be viewed as a class that need to be ta en long term, but some instances of disease free state were seen up to a year after stopping tofacitinib in some dermatological conditions. On this point, dermatologists wanted to see more data on whether duration of treatment and early intervention could affect the natural course of disease or increase time to relapse.

S003 JAK Inhibitors: JAK inhibitors for Atopic Dermatitis: Highly effective oral and topical treatment made easy

After reviewing over 20 Phase III studies for JAK inhibitors, Dr. Eric Simpson (Oregon Health & Science University) outlined some of the general sentiments he came to have about the drugs in this class and how they fit current treatment gaps. Presently, there are several topical therapies to treat atopic dermatitis.

These include corticosteroids and non-steroidal drugs like tacrolimus, pimecrolimus, and crisaborole. There are also systemic therapies that include biologics like dupilumab and those in the pipeline, cyclosporin, methotrexate, mycophenolate, azathioprine, and phototherapy. But with all of these options, there remain unmet needs. For topical therapy, there is a need for more non-steroidal topical therapies that are more potent. So tacrolimus, Elidel, and crisaborole are helpful in the right situation, but they don't have TCS-like efficacy. Additionally, the ideal topical drug would have higher efficacy and not involve significant burning or safety concerns. A topical JAK inhibitor could fill this gap.

The unmet needs for systemic treatments when dupilumab works well are for an oral therapy option that is safe and effective. Cyclosporin and methotrexate are moderately effective and moderately safe, but there is certainly room for something that is safer and more effective than those, with increases EASI90 score that lacks some of the side effects that are seen with the IL-13 blockade drugs, notably conjunctivitis.

Using a biologic to target one or two cytokines is helpful, but if there is a way to block more of the immune activation in atopic

dermatitis patients such an option would be more effective. These pathways involve Th2 cytokines like IL-4, IL-5, IL-10, IL-13, and IL-31, Th1 signaling molecules like IFN-g and IFN-a, Th17 cytokine IL-17, along with some others like IL-22 and TSLP. As of yet, we cannot block multiple cytokines with a biologic. Looking at receptor subunits, heterodimers all use JAK1 to translate their signal down to the nucleus through a JAK/STAT pathway for important cytokine signaling in atopic dermatitis

Targeting JAK1/JAK2, ruxolitinib cream has completed Phase III and appears to fill the gap for a nonsteroidal treatment that may be comparable to a medium potency TCS with minimal application site burning. A medium potency TCS, triamcinolone cream, was used as a comparator in a Phase II dose-ranging study. Results showed a 59.8% reduction in baseline EASI score for triamcinolone at week 4, and 1.5% ruxolitinib cream showed a higher reduction in EASI at the same timepoint meaning this could be as effective as a medium potency steroid. Dr. Simpson did caveat that he uses triamcinolone ointment, which would be a bit more potent. In the identical Phase III TRuE-AD studies, 0.75% and 1.5% ruxolitinib cream, in the absence of TCS, was applied twice daily was compared to placebo in

mild-to-moderate patients who had up to 20% BSA (to limit systemic absorption). Among patients enrolled, around 20% were adolescents and the study had nice diversity with the race of participants being more than 20% black. Additionally, many patients had facial involvement, which Dr. Simpson called out as a nice descriptor since dermatologists focus on using non-steroidal options on this region. Results on the primary endpoint of IGS treatment success showed that significantly more patients treated with ruxolitinib cream achieved this endpoint compared to placebo at week 8, with clear separation occurring at week 4. The high dose, 1.5% twice daily ruxolitinib cream achieved treatment success of 40% at week 4 and over 50% at week 8, compared to up to 15% for placebo. Similarly, ruxolitinib cream demonstrated greater improvement on EASI change from baseline compared to placebo. With regards to itch reduction, patients in the trials started at an average itch NRS score of 5 and achieved at least a 2.8 reduction in itch score, compared to just a 1-point reduction for vehicle. For itch, on day 2 a significant separation from placebo was seen, and in some cases this occurred as early as day 1. This highlights an important point that JAK inhibition may have a direct effect on itch neurons. On safety, there were more total adverse events in vehicle-treated patients than those taking ruxolitinib cream. Importantly, the Phase III results show that application site

burning is not associated with use of this drug, which would be a key differentiator from tacrolimus, pimecrolimus, and crisaborole. Of note, systemic absorption data has yet to be released and would help provide a complete safety picture of this treatment option for dermatologists.

There are three oral JAK inhibitors that could be FDA approved by the end of the year for dermatologists. Baricitinib is already approved in atopic dermatitis in Europe at 2mg and 4mg, the US approval will likely only be for the lower dose. Blocking both JAK1 and JAK2 leads to inhibition of erythropoietin and thrombopoietin, which requires lower dosing to minimize effect on patients' blood count. A black box warning on the package insert for baricitinib, approved for rheumatoid arthritis in the US, lists that serious infections, thrombosis, and malignancies are possible. These are seen in low rates in the rheumatoid arthritis population, which are already at elevated over the general population. JAK1 inhibitor upadacitinib also has a warning for serious infections, thrombosis, and lymphoma. Dr. Simpson called for dermatologists not to overly worry about these warnings, noting that drugs with black box warnings, like methotrexate, are already being used in their patients. Additionally, guidance on how to check labs with these JAK inhibitors will come out, but Dr. Simpson noted that they may

include a one month and then three month follow up to particularly look at complete blood count (CBC), comprehensive metabolic panel (CMP), and cholesterol.

Dr. Simpson believes the efficacy, tolerability, and safety of oral JAK inhibitors depends on the molecule and also on the dose used, but that all three may be appropriate as a first-line systemic option for patients. Some safety and tolerability signals of note include headache, nausea and vomiting, acne, HSV and herpes zoster, serious infection, venous thrombosis, MACE, and malignancy. Of course, the choice to use an oral JAK inhibitor should come after proper patient selection, avoiding elderly patients or those with a history of thrombosis, and shared decision-making with the patient. Additionally, all JAK inhibitors appear to improve itch rapidly, within days of treatment.

Comparative efficacy between the three shows that baricitinib may be the most modest. After 16 weeks of monotherapy, 10-11% are clear or almost clear in the BREEZE-AD1 and -AD2 trials. Though it may be the least effective, baricitinib may be the best tolerated, with very little nausea, vomiting, or headaches and there will be infrequent lab monitoring. The drug is approved to treat atopic dermatitis in Europe at both

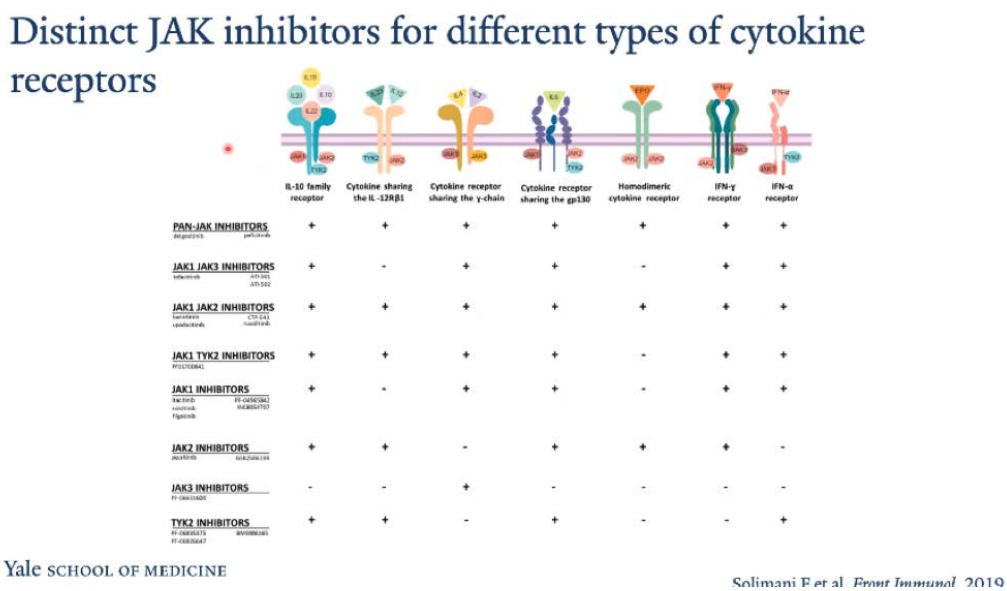
4mg and 2mg doses, but in the US only the lower dose, which saw no venous thrombosis events, is likely to be approved. Looking at how the drug behaves in patient according to baseline BSA involvement shows that the drug is most effective in patients with less than 50% BSA involvement. More extensive BSA of over 50% lead to very low efficacy rates.

JAK1 selective abrocitinib is dosed much higher and in the MONO-1 and -2 studies, 44% and 38% of patients on the highest dose achieved clear or almost clear. The lower 100mg dose is similar to dupilumab and while the higher 200mg dose is likely more efficacious than dupilumab, it was also associated with venous thrombosis (5 events that come out to 0.3/100 person-years). So, a recommendation would be to start patients on the 200mg dose to get them cleared of disease and then drop back to a 100mg maintenance dose. There is a rare but transient platelet reduction that may occur at 4 weeks. A recent publication also showed that the higher dose of abrocitinib was superior to dupilumab at reducing itch at the 2-week timepoint. Notably, on this itch endpoint dupilumab performed similarly to the 100mg dose and eventually catches up and even passes the higher dose over time.

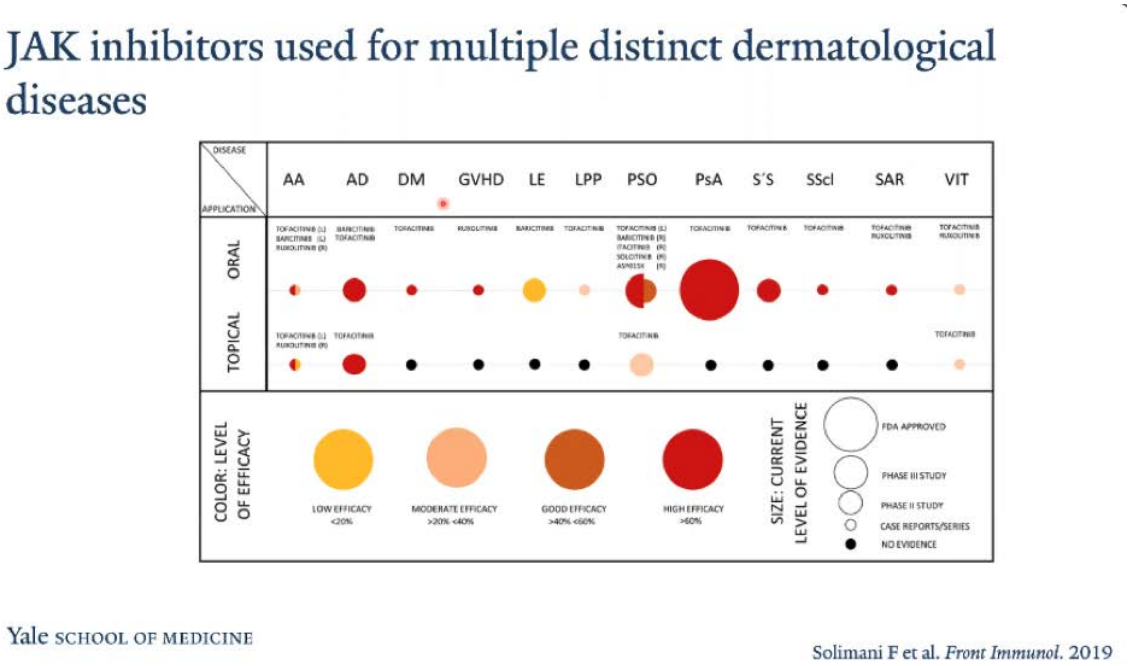
Another JAK1 selective, upadacitinib, achieved the highest efficacy with 62% and 52% of patients on the highest dose achieving clear or almost clear when receiving the drug as monotherapy in the Measure Up 1 and 2 studies. Though the drug is seen as having the highest efficacy, it has the least amount of published safety data. Acne is an adverse event that is uniquely seen with upadacitinib. If the safety profile comes out clean, upadacitinib could be the leader among JAK inhibitors as it beats dupilumab. In the Heads Up trial, evaluating EASI90 at week 16 shows that 61% of patients on 30mg upadacitinib achieved this endpoint as compared to 39% with dupilumab. On complete clearance, PASI100, 28% of patients on upadacitinib achieved this endpoint compared with 8% on dupilumab. There was also a more profound reduction on itch.

S003 JAK Inhibitors: Emerging data for JAK inhibitor treatment of other diseases: How far can JAK inhibitors extend their reach?

Dr. Matthew Vesely (Yale) discussed the potential for Janus Kinase (JAK) inhibitors in other diseases besides those where large clinical trials have been held. He noted that there are many types of cytokine receptors that may be targeted by JAKs and knowing the correct proteins involved is critical in the treatment of a particular disease so that the correct inhibitor can be utilized.



While JAKs are now used for multiple dermatological diseases, Dr. Vesely indicated that this is a fast-moving field and there is potential for disease expansion as well as better efficacy within this drug class.



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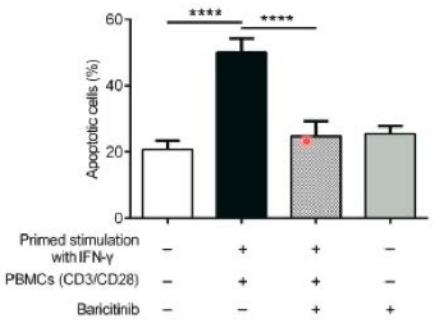
In Part 1 of his presentation, Dr. Vesely discussed the role of JAKs in lichen planus and in drug reaction with eosinophilia and systemic symptoms (DRESS). There is currently a high unmet need in the autoimmune skin disease lichen planus as there are no FDA approved drugs to treat this disease and there are around 700,000 affected in the US. Interferon (IFN)-gamma is one of the key cytokines involved in this indication. He highlighted an article (Shao et al., Sci Trans Med. 2019) in which the addition of baricitinib (JAK1/2 inhibitor) reduced keratinocyte death by apoptosis enhanced by IFN-gamma.



Barictinib (JAK1/2 inhibitor) reduces keratinocyte death by apoptosis by IFN-gamma

Shao S et al. *Sci Trans Med.* 2019

Similarly, Dr. King's group (Damsky et al., JACI 2020) demonstrated that tofacitinib treatment in three patients with severe lichen planus successfully treated disease suggesting at least pre-clinically, that JAK inhibition is an attractive approach to treating this disease. More recently, six months of treatment with tofacitinib has also been shown to demonstrated improvements in nail lichen planus associated with alopecia universalis (Iorizzo and Haneke, JAMA Derm 2021).

Studies indicate there is also an IFN and JAK signature in DRESS that can also be targeted. Dr. Vesely highlighted a case study (Kim et al., Nat Med 2020) wherein a patient with DRESS who previously failed multiple treatments, was administered tofacitinib and over time, was able to taper off steroids and cyclosporin while successfully controlling his disease.

In Part 2 of this discussion, Dr. Vesely discussed JAK inhibitors for sclerosing skin diseases: morphea, systemic sclerosis, and keloids. Based on studies from Dr. King's lab (Damsky et al, JID 2020), p-STAT3 and p-STAT1 were identified in biopsies suggesting these are the immune pathways activated in morphea and can be amenable to JAK inhibition. Indeed, preliminary data in case studies show that treatment with baricitinib and tofacitinib can be effective in patients based on overall scores and activity scores on the Morphea Severity Score scale.

Another emerging area for JAK inhibition is with the treatment of systemic sclerosis, a difficult disease to treat. In 2018, a patient with progressive systemic sclerosis and active painful digital ulcers was treated with tofacitinib which healed the ulcers within two months (Deverapalli and Rosmarin, JEADV 2018). Although the role of JAKs in the treatment of keloids has not been evaluated, Dr. Vesely hypothesized that based on the

pathological signaling pathway of this disease, JAKs and immune modulation could potentially be used for treatment. A study done by Dr. Guttman-Yassky's group showed that keloid lesions had increased IL-4/IL-13 signaling and responded to Th2-targeting dupilumab therapy (Diaz et al, JEADV 2019). Emerging pre-clinical data indicate that in addition to the Th2 pathway, multiple other immune pathways are upregulated in keloids including Th1, Th17/Th22, and JAK3-Skewing (Wu et al, Front Immunol 2020).

Finally, Dr. Vesely ended with Part 3 of his presentation discussing JAK inhibitors as rescue or combination therapy in the context of atopic dermatitis and hidradenitis suppurativa. Although the molecular mechanistic reasoning for combinations are still unknown, Dr. Vesely highlighted one of his atopic dermatitis patients who had recalcitrant lichenified eczematous plaques on certain areas of the body still present during treatment with dupilumab, but cleared when tofacitinib was added to the treatment regimen. Further, even though tofacitinib was tapered off, the patient's plaques were still absent a year later. Similarly, successful cases were seen in patients with recalcitrant hidradenitis suppurativa where tofacitinib was combined with cyclosporin or mycophenolate mofetil suggesting that difficult to treat diseases where TNF monotherapy doesn't totally clear disease, a combination therapy may be needed.