Janus Kinase Inhibitors in the Treatment of Atopic Dermatitis: Military Considerations

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PRACTICE **POINTS**

- Oral Janus kinase (JAK) inhibitors are novel therapies available for the treatment of atopic dermatitis (AD), with multiple recently approved agents within the class.
- Recommended laboratory monitoring during treatment with oral JAK inhibitors may limit the use of these medications in the active-duty military population or in those with special-duty assignments.
- The oral and topical bioavailability of these medications makes them a more feasible option for deploying service members or for those requiring flexible dosing.
- The rapid improvement in AD seen in multiple trials of oral JAK inhibitors suggests these agents could prove useful in management of acute AD flares, especially in military environments, where injectable agents are either unavailable or unsupported.

Janus kinase (JAK) inhibitors represent one of the newest and most promising additions to the available treatments of atopic dermatitis (AD). Janus kinase inhibitors offer several key benefits over injectable biologics to include more predictable pharmacokinetics, nonimmunogenicity, and flexible dosing, in addition to their oral and topical bioavailability. Recommended laboratory assessments before and during treatment in addition to medication side effects may limit the scope of use in the active-duty military population and specifically within special-duty populations. In this article, we review approved and emerging JAK inhibitors for the treatment of AD as well as important considerations for both military and nonmilitary patient populations.

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The atopic dermatitis (AD) therapeutic landscape is changing considerably with the advent of Janus kinase (JAK) inhibitors. Several JAK inhibitors recently have been approved by the US Food and Drug Administration, building off years of foundational research aimed at elucidating the downstream effects of the JAK–signal transducer and activator of transcription (STAT) pathway and its role in AD pathogenesis. Agents within this promising new class of drugs have performed well vs placebo in phase 2 and 3 clinical trials. This article reviews relevant trial efficacy and safety data of several JAK inhibitors as well as the implications of the use of these medications in AD patients, with specific considerations unique to active-duty military personnel.

Background on JAK Inhibitors

The hematopoietin superfamily of cytokine receptors encompasses a broad group that includes receptors for immune (eg, IL-2, IL-4, IFN-γ), hematopoietic (eg, erythropoietin, thrombopoietin, granulocyte-macrophage colony-stimulating factor), and nonimmune (eg, prolactin, leptin, growth hormone) cytokines. These cytokines signal via the JAK-STAT pathway. The hematopoietin family of cytokine receptors lacks intrinsic enzymatic activity, and as a result, they rely on JAK enzymes to transmit their signals intracellularly after cytokine binding to the receptor.[1] Janus, of Roman mythology, was the god of doorways and archways and was commonly depicted with 2 heads. Janus kinases were named for their 2 "faces," the kinase domain with its adjacent regulatory kinaselike domains.[2] The binding of a cytokine to its receptor triggers engagement of the receptor by JAKs, leading to phosphorylation of both the JAKs and the receptor. Subsequent recruitment and phosphorylation of STAT proteins occurs. Following STAT phosphorylation, the STAT proteins dissociate, dimerize, and translocate to the nucleus, where they enact changes in cell behavior through transcriptional effects.[1]

Humans possess only 4 JAKs. Janus kinase 1, JAK2, and tyrosine kinase 2 are widely expressed, whereas JAK3 expression is largely limited to immune cells. Thus, there

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is notable overlap in the use of the 4 JAKs among the relatively larger number of various cytokines that utilize them to propagate intracellular signaling.[1] Janus kinase 1 is important for signaling of receptors activated by a variety of interleukins, as well as IFN-α, IFN-β, and IFN-γ. Janus kinase 2 is important for signaling for the hormone-like cytokines erythropoietin, thrombopoietin, growth hormone, granulocyte-macrophage colony-stimulating factor, IL-3, and IL-5. Janus kinase 3 is important for hematopoietic cell proliferation and function.[1]

JAK Inhibitors and Atopic Dermatitis

Topical treatments, including corticosteroids and calcineurin inhibitors, are considered the standard-of-care therapy for most patients with AD; however, their clinical benefit often is limited by their anatomic use restrictions and local adverse events, including skin atrophy, striae, and application-site reactions such as stinging and burning.[3] As a result, long-term application of these drugs, particularly in sensitive areas, is not recommended owing to safety/tolerability issues.[3] Systemic immunomodulatory medications are indicated for patients with AD who do not achieve adequate disease control with topical treatments and/or phototherapy or for patients with severely impaired quality of life.[4]

Janus kinase inhibitors have several key benefits over biologics: oral and topical bioavailability, predictable pharmacokinetics, nonimmunogenicity, and dosing flexibility.[4] Janus kinase 1 is central to the cell signaling of many cytokines involved in the pathogenesis of AD that comprise the T-helper lymphocytes type 2 axis: IL-4, IL-13, and thymic stromal lymphopoietin. Janus kinase signaling also may mediate itch responses by acting directly on sensory nerve fibers. Consequently, the substantial reduction in pruritus seen in many studies of JAK inhibitors is thought to be in part due to the effects on sensory nerve fibers in the skin and the blockade of early itch signaling in response to IL-4, IL-13, and IL-31.[5]

Abrocitinib is a JAK1 inhibitor with a similar side effect profile to upadacitinib. Both agents were approved by the FDA for the treatment of refractory moderate to severe AD on January 14, 2022.[6] These are second-generation (also referred to as selective) oral JAK inhibitors with much greater inhibitory potency for JAK1 than for JAK2, JAK3, or tyrosine kinase 2, thereby reducing the risk for hematopoietic effects associated with JAK2 inhibition. The approval of abrocitinib stemmed from the phase 3 clinical trial JAK1 Atopic Dermatitis Efficacy and Safety (JADE)-MONO-1 (N=387),[7] its replicate trial JADE-MONO-2 (N=391),[8] and the JADE COMPARE trial.[9] The JADE-MONO trials were multicenter, double-blind, placebo-controlled studies that enrolled patients 12 years and older with moderate to severe AD.[7,8] Treatment groups consisted of 100-mg and 200-mg doses and were evaluated with the placebo group for their ability to achieve an investigator global assessment (IGA) score of 0 or 1 and eczema area and severity index 75 (EASI-75) at 12 weeks.[7,8] Sixty-three percent of patients in the 200-mg group, 40% in the 100-mg group, and 12% in the placebo group reached the EASI-75 end point, and the differences in these response rates were statistically significant vs placebo (100 mg: 27.9% [95% CI, 17.4-38.3], $P<.0001$; 200 mg: 51.0% [95% CI, 40.5-61.5], $P<.0001$). Notably, 44% of patients using the 200-mg dose achieved almost complete or complete resolution of AD (IGA responders, improvement of ≥2 and IGA score of 0 or 1 at 12 weeks).[7] In JADE-MONO-2, EASI-75 also was achieved significantly more frequently in the treatment groups compared with the placebo group at 12 weeks (200 mg: 61.0%; 100 mg: 44.5%; placebo: 10.4%; $P<.001$ vs placebo).[8] Adjunctive therapy with topical corticosteroids was prohibited in both studies. A dose-dependent decrease in platelets was seen in both trials, as in the phase 2 trial that preceded them.[10]

The primary end point of the JADE COMPARE trial was to evaluate the efficacy of abrocitinib as compared with placebo at 12 weeks in adult patients with moderate to severe AD and in the setting of concomitant topical corticosteroid therapy.[9] One of several secondary end points of this study compared the ability of dupilumab vs abrocitinib and placebo treatment groups to achieve itch reduction at 2 weeks, defined as 4-point improvement or more from baseline in the score on the Peak Pruritus Numerical Rating Scale (NRS), a well-defined, reliable, sensitive, and valid scale for evaluating worst itch intensity in adults with moderate to severe AD.[9,11] The primary end point was the same as in the other phase 3 studies and was met in the JADE COMPARE trial by all treatment arms. An EASI-75 was seen in 70.3% of patients treated with 200 mg of abrocitinib, 58.7% in the 100-mg abrocitinib group, 58.1% in the dupilumab group, and 27.1% in the placebo group ($P<.001$ for both abrocitinib doses vs placebo). Only the 200-mg dose of abrocitinib demonstrated superior itch response at week 2 compared with dupilumab (22.1% response rate difference [95% CI, 13.5-30.7; $P<.001$]). Both abrocitinib groups failed to demonstrate significant differences compared with dupilumab with respect to other secondary end points to include IGA response and EASI-75 at week 16.[9]

The most frequently reported treatment-associated adverse events were nausea, nasopharyngitis, upper respiratory tract infection, and headache, and the percentages were similar among trial groups.[9] Acne was more frequently reported in the abrocitinib groups compared with placebo and the dupilumab group, and conjunctivitis was more frequently reported in the dupilumab group. Herpesvirus cutaneous infections were rare in the abrocitinib groups, as were other serious infections. No deaths, major adverse cardiovascular events (MACEs), or venous thromboembolic events (VTEs) occurred during the trial. Dose-dependent increases in creatinine phosphokinase were seen in the abrocitinib groups, whereas dose-dependent decreases were seen in platelet counts, with no patient demonstrating a platelet count below 75,000/mm^3 during the study.[9] Low-density lipoprotein

cholesterol levels and high-density lipoprotein cholesterol levels increased in a dose-dependent manner as well, but the ratios of low-density lipoprotein to high-density lipoprotein were unchanged.[9] The results of a phase 3, 92-week extension study, JADE EXTEND, were recently published and demonstrated a role for abrocitinib as a treatment for patients with moderate to severe AD, regardless of prior dupilumab response status.[12]

Upadacitinib, another selective JAK1 inhibitor, was approved following data from 2 replicate double-blind, phase 3, randomized, controlled trials—Measure Up 1 and Measure Up 2.[13] Results demonstrated that monotherapy with once-daily upadacitinib 15 mg or 30 mg is an effective and well-tolerated treatment option for patients with moderate to severe AD vs placebo. All coprimary end points at week 16 were achieved in the upadacitinib groups in both trials. Acne, upper respiratory tract infections, nasopharyngitis, headache, and increase in serum creatinine phosphokinase levels were the most frequently reported adverse events. Rates of herpes zoster infection in upadacitinib groups were low.[13]

In the subsequent phase 3 AD Up trial, researchers evaluated the safety and efficacy of combination therapy with topical corticosteroids in patients aged 12 to 75 years.[14] Upadacitinib groups again achieved the identical coprimary end points that were present in the Measure Up trials[13] as well as all key secondary end points.[14] Additionally, significant differences in secondary end points, such as a 4-point improvement in the Worst Pruritus NRS vs placebo, were noticed in both upadacitinib treatment groups as early as 1 week into the study ($P<.0001$), with maintenance of the effect through to week 16 ($P<.0001$).[14] AD Up was followed by the Heads Up trial, a 24-week, phase 3, multicenter, double-blind, randomized, controlled trial comparing safety and efficacy of upadacitinib with dupilumab among 692 adults with moderate to severe AD.[15] At week 16, a higher percentage of patients in the upadacitinib group achieved EASI-75 vs the dupilumab group (71.0% vs 61.1%, respectively; $P=.006$). The difference noted at week 2 was even more impressive, with 43.7% of patients in the upadacitinib treatment group achieving EASI-75 compared with 17.4% in the dupilumab group ($P<.001$). No new safety-related events were registered compared with the already available data for both drugs.[15]

Ruxolitinib (RUX) is a topical JAK1 and JAK2 inhibitor that was FDA approved in September 2021 for the treatment of AD.[16] In a phase 2 clinical trial of 307 adult patients with 3% to 20% body surface area (BSA) affected with AD, significant reductions in itch NRS scores were observed within 36 hours after the first application of RUX cream 1.5% twice daily (-1.8 vs -0.2, $P<.0001$).[17] These decreases were noted within the first 2 weeks of treatment for all the RUX cream regimens and were sustained through to week 8, the end of the double-blind period. At 4 weeks, change in itch from baseline was significantly reduced in the RUX 1.5% twice-daily group compared with the triamcinolone ointment 0.1% group (−4 vs −2.5, $P=.003$). During the open-label treatment period from 8 to 12 weeks, all patients who switched to RUX cream 1.5% twice daily noted further reductions in itch, and those who continued it demonstrated additional improvement.[17]

The recent FDA approval was further backed by positive phase 3 trial data from the TRuE-AD1 and TRuE-AD2 studies.[18] Patients in these trials were aged 12 years and older and had AD for 2 or more years with an IGA score of 2 or 3 and 3% to 20% affected BSA. Patients were randomized to twice-daily RUX cream 0.75%, RUX cream 1.5%, or vehicle cream, and the primary end point was an IGA score of 0 or 1 and an improvement of 2 or more points from baseline at week 8. Significantly more patients achieved IGA treatment success with RUX cream 0.75% (TRuE-AD1, 50.0%; TRuE-AD2, 39.0%) and RUX cream 1.5% (TRuE-AD1, 53.8%; TRuE-AD2, 51.3%) vs vehicle (TRuE-AD1, 15.1%; TRuE-AD2, 7.6%; $P<.0001$) at week 8. The RUX groups experienced dramatically reduced itch compared with vehicle, with a mean reduction of approximately 3 points on the NRS at 8 weeks. Additionally, statistically significant itch reductions vs vehicle were reported within 12 hours of first application of RUX cream 1.5% ($P<.05$). Application-site reactions including stinging and burning occurred in less than 1% of patients, and none were considered clinically significant. Mean plasma concentrations of RUX were monitored during the phase 2 and 3 AD studies and did not lead to any clinically meaningful changes in hematologic parameters. The low bioavailability following topical application of RUX cream (6% in the TRuE-AD studies) allows for a targeted delivery of the active drug to lesional skin while reducing the safety issues associated with oral administration of JAK inhibitors.[18]

Baricitinib is a predominantly JAK1 and JAK2 inhibitor that was the first JAK inhibitor to be approved for the treatment of moderate to severe AD in the European Union and Japan.[19] Although the FDA's decision on baricitinib has lagged behind market competitors, in 2 phase 3 clinical trials, BREEZE-AD1 and BREEZE-AD2, baricitinib demonstrated benefit over placebo on clinically important measures of disease severity. The primary end point—the proportion of patients achieving an IGA score of 0 or 1 with an improvement of 2 or more points from baseline at week 16—was met by both tested doses of baricitinib (2 mg and 4 mg) vs placebo in BREEZE-AD1 (2 mg, $P\leq.05$; 4 mg, $P\leq.001$) and BREEZE-AD2 (2 mg, $P\leq.05$; 4 mg, $P\leq.001$). In addition, baricitinib 4 mg consistently demonstrated significant benefit over placebo on other clinically important measures of disease severity at week 16 to include itch (BREEZE-AD1 and BREEZE-AD2, $P\leq.001$), sleep disturbance (BREEZE-AD1, $P\leq.01$; BREEZE-AD2, $P\leq.001$), and skin pain (BREEZE-AD1, $P\leq.01$; BREEZE-AD2, $P\leq.001$). Nasopharyngitis, upper respiratory tract infections, creatine phosphokinase elevations, and headaches were the most frequently reported adverse events. During the 16-week treatment period

in these trials, no deaths, MACEs, or VTEs occurred.[19] Similar results were seen in a long-term extension study, BREEZE-AD3.[20] The combination of baricitinib and topical corticosteroids were evaluated in 2 additional phase 3 trials, BREEZE-AD4[21] and BREEZE-AD7.[22] Although only baricitinib 4 mg met the primary end point of EASI-75 at week 16 in both trials, both dosing regimens plus topical corticosteroids demonstrated notable reduction in multiple clinical and quality-of-life indices prior to week 2 when compared with placebo plus topical corticosteroids.[22,23]

AD in Military Service Members

Atopic dermatitis is a common condition in the general population, with a prevalence of 7.3% (95% CI, 5.9-8.8) in a recent study of American adults.[24] Historically, the burden of AD that would be expected among active-duty military service members given the prevalence among the general population has not been observed, in part because of the disqualifying nature of AD for enlistment.[25] The Department of Defense Instruction 6130.03, Volume 1, Medical Standards for Military Service: Appointment, Enlistment, or Induction stipulates that a history of AD or eczema after the twelfth birthday or history of residual or recurrent lesions in characteristic areas (ie, face, neck, antecubital or popliteal fossae, occasionally wrists and hands) is disqualifying.[26] Specific military services possess additional standards that further define limits within the aforementioned Department of Defense instruction.[25] Additionally, there are service-specific policies in place that mandate medical evaluation boards to determine fitness for continued service in the event the condition interferes with the member's ability to perform their duties. In section 4.2 of the U.S. Navy Aeromedical Reference and Waiver Guide, further restrictions for aviation personnel are delineated: "Depending on the location of lesions, there can be interference with the wearing of flight gear. The symptoms, particularly itching, can be distracting in flight. Patients with atopic dermatitis are more susceptible to contact dermatitis due to irritants found in a military environment." Ultimately, the document stipulates that symptom severity and the requirement for therapy will determine the aeromedical disposition. It specifically states that "[p]atients controlled on topical therapy over small areas and patients who are asymptomatic on stable doses of loratadine (Claritin) OR fexofenadine (Allegra) may be considered for waiver," and "intermittent use of topical steroids over a limited area is compatible with waiver."[27] It follows that limited use of topical JAK inhibitors, such as RUX, would be compatible with a waiver, given the favorable side effect profile and requirement for use in patients with 20% or lower affected BSA.[16] This is just one example of duty-specific and service-specific medical standards that exist that could impact the use of both topical and oral JAK inhibitors.

Use of oral JAK inhibitors in active-duty service members is less ideal for multiple reasons. A large randomized safety clinical trial of patients with rheumatoid arthritis who received tofacitinib and methotrexate was required by the FDA to evaluate the risk of MACEs, malignancy, and infections associated with JAK inhibitor treatment. Data from this trial showed a dose-dependent increased risk for MACEs, all-cause mortality, and thrombosis at both doses of tofacitinib compared with tumor necrosis factor inhibitors and a non–dose-dependent increased risk for malignancy excluding nonmelanoma skin cancer.[28] In contrast to the MACE and VTE data from patients with diseases other than AD treated with JAK inhibitors, there has been only 1 patient who developed a pulmonary embolism while being treated with baricitinib 4 mg.[22,29] Downstream effects from the above study were label recommendations to reserve the medicines for patients who had an inadequate response or intolerance to 1 or more tumor necrosis factor blockers and to carefully consider risks vs benefits in patients, in particular current or prior smokers, those with other cardiovascular risk factors or a history of VTE, and those with a malignancy history other than already treated nonmelanoma skin cancer.[28]

There are consistent observations of laboratory abnormalities with JAK inhibitors, as discussed above, to include creatine phosphokinase elevation and cytopenias.[30] Although existing data demonstrate that cytopenias are less of a concern in the AD population compared with the rheumatoid arthritis population, baseline and periodic laboratory monitoring are still recommended. In general, pretreatment laboratory assessment prior to initiating an oral JAK inhibitor should consist of a complete blood cell count with differential, complete metabolic panel, tuberculosis screening, chronic hepatitis panel, HIV screening, and a fasting lipid panel.[2] The feasibility of obtaining these laboratory measurements in an operational setting or sea-going platform is limited, but many deployed locations and naval vessels possess the laboratory capability to perform a complete blood cell count and complete metabolic panel. Overall tolerability of oral JAK inhibitors in the treatment of AD appears favorable based on studies that were mostly 16 weeks in duration. Few recent longer-term studies have confirmed this side effect profile, but additional studies are needed.

Final Thoughts

Janus kinase inhibitors are a promising therapeutic class with multiple recently FDA-approved agents for the treatment of moderate to severe AD, with new agents on the horizon. Available efficacy data are promising and balanced by a favorable safety profile in clinical trials to date. The oral and topical bioavailability of JAK inhibitors makes them attractive alternatives to existing therapies. The rapidity of itch reduction and AD improvement demonstrated in multiple trials has the potential to decrease the length of limited-duty assignments, potentially returning treated service members to full-duty status more expeditiously. Other applications include use of these medications in scenarios where injectable medications are either unavailable or unsupported.

In the active-duty population, both the condition and/or the treatment may be duty limiting. Service members with AD who require more than topical treatment may require a medical evaluation board to determine if they are still fit to serve. The deployed environment routinely exacerbates AD and exposes service members to infections and environments where immunosuppression can create more risks than in the general population. Nonbiologic medications, which do not require refrigeration, are an exciting option for our patients with AD, including those actively serving or considering serving in the military. However, all factors in any patient's life should be considered. Therefore, it is important for the nonmilitary dermatologist to work with local military physicians and the patient to determine the optimal treatment regimen to result in the best possible outcome.

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