Janus kinase inhibitors in dermatology: A systematic review

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Background: Janus kinase (JAK) inhibitors are emerging as a promising new treatment modality for many inflammatory conditions.

Objective: Our aim was to systematically review the available data on the use of JAK inhibitors in cutaneous diseases.

Methods: This is a systematic review of PubMed and ClinicalTrials.gov.

Results: One hundred thirty-four articles matched our search terms, of which 78 were original articles and 12 reports on adverse events. Eighteen clinical trials were found. JAK inhibitors have been extensively studied for psoriasis, showing beneficial results that were comparable to the effects achieved by etanercept. Favorable results were also observed for alopecia areata. Promising preliminary results were reported for vitiligo, dermatitis, graft versus host disease, cutaneous T cell lymphoma, and lupus erythematosus. The most common adverse events reported were infections, mostly nasopharyngitis and upper respiratory tract infections.

Limitations: It was not possible to perform a meta-analysis of the results.

Conclusions: This systematic review shows that while JAK inhibitors hold promise for many skin disorders, there are still gaps regarding the correct dosing and safety profile of these medications for dermatologic indications. Additional trials are necessary to address these gaps. (J Am Acad Dermatol 2017;76:745-53.)

Key words: alopecia areata; atopic dermatitis; baricitinib; dermatology; graft versus host disease; JAK inhibitors; psoriasis; ruxolitinib; tofacitinib; vitiligo.

Recent years have brought great progress in our understanding of the pathogenesis of inflammatory and immunologic diseases, thereby uncovering novel therapeutic targets. One of these newly identified targets is the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, which is pivotal for the downstream signaling of inflammatory cytokines and of different growth factors. JAKs belong to the group of the cytoplasmic tyrosine kinases. They are activated after stimulation of several cellular receptors by their specific growth factors, growth hormones, chemokines, and cytokines. After activation, they phosphorylate STAT transcription factors, resulting in the transportation of STAT factors to the nucleus, affecting expression of specific genes. There are 4 known types of JAKs: JAK1, JAK2, JAK3, and TYK2, expressed mainly in hematopoietic cells.[1,2]

The realization that JAKs contribute substantially to the immunologic processes in inflammatory diseases (eg, rheumatoid arthritis [RA],[3] ankylosing spondylitis,[4] and inflammatory bowel disease[5]) led to the development of JAK inhibitors as therapeutic immunosuppressive agents. At present, 2 JAK inhibitors have been approved by regulatory agencies, and additional compounds are being developed and

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tested. In 2011, ruxolitinib, a JAK1/2 inhibitor, was approved by the US Food and Drug Administration (FDA) for myelofibrosis,[6] and was later approved in other countries for the same indication. Tofacitinib, which is mainly directed against JAK1/3,[7] was recently approved in several countries for the treatment of RA.[8]

The interest of the dermatology field in JAK inhibitors has been piqued mainly because of the large clinical trials that were performed with tofacitinib and are being performed with other JAK inhibitors for psoriasis. Alopecia areata (AA) is another condition that showed promising results from treatment with JAK inhibitors. Other immunologic diseases with cutaneous manifestations that are being studied include vitiligo, atopic dermatitis (AD), graft versus host disease (GVHD) and lupus erythematosus (LE; Table I). Because of the constantly accumulating literature on JAK inhibitors in dermatology, there is a need for a current and comprehensive summary on their use in patients with cutaneous conditions. Therefore, we performed a systematic review on the use of JAK inhibitors in cutaneous diseases, describing their regimen, efficacy, and adverse events (AEs).

CAPSULE SUMMARY

- There is increasing evidence that Janus kinase inhibitors may effectively treat a variety of inflammatory skin diseases.
- This systematic review includes a summary of studies exploring their use in psoriasis, alopecia areata, and a variety of other skin conditions.
- Janus kinase inhibitors have the potential to significantly impact dermatologic therapy, although more data regarding their safety and efficacy are needed.

METHODS

A systematic review of studies describing the use of JAK inhibitors in dermatologic disorders was performed. We performed an electronic literature search of PubMed database on JAK inhibitors and dermatology twice—in January 2016 and in November 2016. The references of each relevant article were also reviewed. In addition, clinical trials were searched using ClinicalTrials.gov in October 2016. The methodology of the systematic search is described in Fig 1.

RESULTS

Our first search in January 2016 yielded 278 PubMed database results. The same search performed 10 months later (November 2016) found 439 results, a 58% increase. Three hundred five search results were excluded because of duplications (articles that appeared twice using different types of search words) or because they did not focus on JAK inhibitors and dermatology. One hundred thirty-four articles matched our search terms, and consisted of 44 reviews, 78 original articles (53 clinical studies and 25 in vitro and in vivo preclinical studies), and 12 reports on AEs (Fig 1; Supplemental Table I; available at http://www.jaad.org). All studies were in English, except 1 review article that was published in French. In addition, at least 18 clinical trials are still ongoing or not yet published (Supplemental Table II; available at http://www.jaad.org). Psoriasis and psoriatic arthritis (PsA) were the most common diseases evaluated among the original clinical studies (43%) and clinical trials (39%). Dermatitis was the most prevalent condition evaluated in preclinical studies (Supplemental Table I).

Psoriasis

Thirty-four studies on the effect of JAK inhibitors in psoriasis and PsA were found, consisting of 4 preclinical studies, 23 original clinical studies, and 7 clinical trials (Table II; available at http://www.jaad.org). In 79% of the studies, tofacitinib was the drug that was assessed.

Tofacitinib has a regulatory effect on the synovial inflammatory process in PsA samples.[9] In addition, when examined in an in vitro model of psoriasis, it reduced expression of JAK1 and 3.[10] SAR-20347, a JAK1 and TYK2 inhibitor, and R-348, a JAK3 inhibitor, were tested on psoriatic murine models, resulting in lesional improvement accompanied by decreased levels of proinflammatory cytokines.[11,12] The dosage of oral tofacitinib for plaque-type psoriasis was evaluated in a phase 1 study, using a range of doses (5-50 mg twice daily or 60 mg once daily). All doses except for the 5 mg twice daily dose resulted in improvement in psoriatic lesions when compared to placebo.[13] Two large phase 3 studies demonstrated a 75% reduction in Psoriasis Area and Severity Index scores (PASI75) and physician's global assessment (PGA) scores for both the 5 and 10 mg doses given twice daily for 16 weeks in comparison to placebo.[14] The PASI75 rates were better for the 10 mg twice daily dose than for the 5 mg twice daily dose (approximately 40% and 60%, respectively). Pruritus improved rapidly with both doses of tofacitinib, as soon as 1 day after starting the drug.[15] Withdrawal after 24 weeks of tofacitinib resulted in >70% reduction in the proportion of patients with PASI75, which were regained in most of the patients