



Various Application of Tofacitinib and Ruxolitinib (Janus Kinase Inhibitors) in Dermatology and Rheumatology: A Review of Current Evidence and Future Perspective

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ABSTRACT **Introduction:** Janus kinase inhibitors (JAKi) are anti-inflammatory medications suppressing Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway by inhibiting various cytokines receptors on the membrane of cells. Mutations and polymorphisms on JAK and STAT proteins can cause dysregulation in the balance of immune system, and ultimately result in autoimmune disorders.

Objectives: To record and summarize the overall efficacy and safety of JAKi in various autoimmune conditions such as alopecia areata (AA), psoriasis vulgaris (PV), psoriatic arthritis (PsA), atopic dermatitis (AD), vitiligo, hidradenitis suppurative (HS), lichen planus (LP), and pyoderma gangrenosum (PG).

Methods: A thorough review of articles was performed across PubMed and Google Scholar on meta-analyses, systematic reviews, clinical trials and case studies evaluating the treatment of autoimmune disorders such as AA, PV, PsA, AD, vitiligo, LP, HS, and PG with JAKi. Duplicated data and animal experiments or in vitro/ex vivo studies were excluded.

Results: All the reviewed articles reported beneficial effects of tofacitinib and ruxolitinib application in the treatment of disorders mentioned above with the autoimmune predisposition.

Conclusions: Tofacitinib and ruxolitinib showed potential efficacy in treating several autoimmune disorders. Based on records in the reviewed studies, both medications had acceptable safety profiles; however, physicians are recommended to outweigh the risks and benefits of such treatments for each specific condition.

Introduction

The Janus kinase inhibitors are a category of anti-inflammatory medications, targeting JAK-STAT pathways. Many inflammatory cytokines function through the JAK-STAT pathways in the human body [1,2]. Cytokines are crucial molecules working on the immune system regulation, and their dysregulation might be important in the pathogenesis of autoimmune disorders [3].

Genetic polymorphisms and different mutations can occur within JAK-STAT pathways, resulting in several forms of malignancies and autoimmune disorders, ie polymorphisms of JAK2 and STAT3 are involved in psoriasis [4]. JAKi medications provide us with the possibility of shutting down the impaired JAK-STAT pairs. Ruxolitinib and tofacitinib are the prototypes of JAKi. Ruxolitinib is a JAK1/2 selective inhibitor; it affects several parts of the innate and adaptive immune system, including natural killer cells (NKc), dendritic cells, T-helpers, and regulatory T-cells [5]. Tofacitinib preferentially blocks JAK1/3 and, to some degree, JAK2 and TYK2 [6].

JAKi, like other medications, have adverse effects (AEs) on the human body. JAKi suppress the immune system at some levels, and their consumption increases the risk of some infections such as herpes zoster (HZ). Vaccination against HZ prior to the treatment with tofacitinib is recommended. Non-HZ opportunistic infections, including cytomegalovirus, cryptococcus, histoplasmosis and clostridium difficile are also reported in JAKi recipients [5,7].

There is a potential risk of increasing venous thromboembolism (VTE) events following the treatment with JAKi so it is recommended to avoid prescribing JAKi in patients with age >50, previous VTE, hypercoagulability, smoking, cardiovascular disease (CVD), long-term immobilization, recent trauma or surgery, paralysis, malignancy, obesity, frequent long flights, and hormonal therapy. A further consideration is required to either avoid or prescribe JAKi with extra caution in patients with a history of cancer; however, there is not enough evidence and data about the carcinogenicity of JAKi. Other AEs include anemia, reversible hyperlipidemia and minimal elevation in liver transaminases and creatine phosphokinase (CPK) [7,8].

Objectives

The development of JAKi in dermatology and rheumatology is still in the early stage; however, there is favorable evidence about the utility of JAKi in treating some of the autoimmune disorders. To prevent extensive efforts collecting data from different studies to answer specific inquiries about such disorders and medications, we performed a narrative review to summarize all the available evidence on the utility of JAKi in treating AA, PV and PsA, AD, vitiligo, LP, HS, and PG.

Methods

A thorough search was performed on PubMed, and Google Scholar using combinations of the following MeSH terms: “tofacitinib,” “ruxolitinib,” “JAK inhibitors,” “Janus Kinase inhibitors,” “alopecia areata,” “psoriasis vulgaris,” “psoriasis arthritis,” “atopic dermatitis,” “vitiligo,” “hidradenitis suppurative,” “pyoderma gangrenosum,” “lichen planus,” “lichen planopilaris.” A total of 672 publications were found. After removing duplicates and non-suitable publications, we focused on the most recent and available pooled studies such as systematic reviews and meta-analyses and then available clinical trials, observational and case studies.

Results

Alopecia Areata

Alopecia areata is a non-cicatricial alopecia with an autoimmune etiology, affecting approximately 2% of the general population. Histopathology assessment on the involved skin showed lymphocytic infiltration around the hair follicles at the level of bulb or lower [9]. Immune system dysregulation results in hair follicles damage by T-cells and NKc. Moreover, auto-re-activation of immune cells upregulates IFN- γ and cytokines and cause further cellular damage and inflammation [10].

Excessive activation of JAK-STAT has a major effect on maintaining the activation of CD8+ T-cells and NKc. Additionally, a low level of T-regulatory cells identified in AA patients, makes it impossible to suppress excessive amounts of cytokines. These complexes of immune dysregulations contribute to hair follicles damage [10,11].

Yu et al reviewed 12 studies with 346 patients. In this review 288 participants received oral tofacitinib and 58 received oral ruxolitinib. The outcome measurement was reported with the Severity of Alopecia Tool₅₀ (SALT₅₀), showing 66% overall improvement in all patients. There was no statistically difference when studies categorized by sex, age and subtypes of AA (P = 0.81, P = 0.37 and P = 0.91, respectively). The SALT₅₀ rates were lower in patients who received a shorter length of treatment but was not statistically significant (P = 0.25). The reported AEs were upper respiratory tract infections (URTI), urinary tract infections (UTI), herpes simplex and herpes zoster infections, alteration of blood cells count, the elevation of liver aminotransaminase and lipids; moreover, there were no fatal AEs [12]. In another meta-analysis, Hamilton et al reviewed ten different studies on the systemic and topical tofacitinib and ruxolitinib in children and teenage populations (age 1 – 17 years). The review affirmed success for JAKi in children and teens with higher numbers of complete responders and smaller numbers of poor responders compared to adults. AEs were small and limited to mild infections, diarrhea and reversible lab abnormalities [13]. In addition, Guo et al conducted a meta-analysis on 14 studies with 275 patients treating with oral and topical tofacitinib. A complete response in 54.0% and partial response in 26.1% of patients were reported. The AA relapse rates were 24.0% in the pooled results, and the main reason was medication discontinuation. A 7.2% of patients presented AEs, and the most common AE was URTI [14].

Psoriasis Vulgaris

Psoriasis is a chronic autoimmune inflammatory disease with the prevalence of 2% worldwide. Psoriasis has several subtypes, including plaque, guttate, inverse, and pustular. Over-activation of dendritic cells is responsible for the initial phase of psoriasis and unbalanced elevated levels of cytokines such as IL-17, IL-21 and IL-22 (mostly Th17 and IL-23 driven [15]) for the maintenance phase of inflammation. Medications such as tofacitinib and ruxolitinib targeting TNF- α , IL-23 and IL-17 and JAK/STAT pathways can be effective in treating PV [16].

Kvist-Hansen et al conducted a systematic review on five clinical trials (phase two and three trials) utilizing oral tofacitinib to treat moderate to severe forms of PV. The effectiveness was calculated based on PASI75 (Psoriasis Area & Severity Index 75% reduction). In the phase two studies, the effectiveness of tofacitinib was reported 25% with 2 mg/bid, 40.8% with 5 mg/bid, and 66.7% with 15 mg/bid compared to 2% efficacy in placebo. In the phase three studies, the effectiveness was reported 39.5% – 54.3% with 5 mg/bid and 59.2% - 81.1% with 10 mg/bid compared to 5.6% - 12.5%

for the placebo recipients at weeks 16 - 24. Moreover, clinical efficacy was reported based on Dermatology Life Quality Index (DLQI) and Nail Psoriasis Severity Index (NPSI). AEs such as hyperlipidemia, CPK elevation, anemia and lymphopenia were observed in some patients [17].

Tian et al meta-analyzed seven randomized clinical trials (RCTs) about oral tofacitinib in chronic plaque psoriasis. Physician global assessment (PGA) and PASI 75 (4 studies reported PASI 90) showed denoting difference between the group of tofacitinib 5 mg/bid users and control group (P < 0.00001). The effectiveness of tofacitinib 10 mg/bid was also significantly distinct from the control group (P < 0.00001). Moreover, 5 mg/bid of tofacitinib showed less efficacy than 10 mg/bid. Even though, there was no statistically significant difference in AEs between 5 and 10 mg tofacitinib, more AEs were related to 10 mg/bid dosage [18]. Further, it is recommended to conduct clinical trials on topical types of JAKi in treating PV.

Psoriatic Arthritis

Approximately 19.4% of patients with psoriasis present joints involvement [19]. PsA manifestations include peripheral arthritis, enthesitis, axial disease, dactylitis, and skin characteristics [20]. No serology markers are available to distinguish PsA from psoriasis; however, hyperlipidemia, gout, axial spondylopathy or allergic rhinitis are more common in PsA [19].

Companaro et al systematically reviewed three RCTs studying oral tofacitinib. In these studies, 947 patients treated with tofacitinib and those who only received 5 mg/bid were assessed in the review. The results at week 16 revealed a significant higher ACR20 (number of patients who achieved $\geq 20\%$ response rate to the treatment based on the American College of Rheumatology Index) response than placebo. Moreover, tofacitinib also presented statistically higher ACR50, ACR70 and PASI75 response rates compared to placebo, and Health Assessment Questionnaire-Disability Index (HAQ-DI) score and post-treatment fatigue assessment showed lower rate, which means better response. Serious AEs were greater in the treatment group than the control group; however, it was not proved statistically [21].

Paik et al reviewed tofacitinib efficacy in two well-designed parallel RCTs (phase 3) in PsA patients: the OPAL Broaden with 442 patients for 12 months and the OPAL Beyond with 394 patients for six months. Patients received tofacitinib 5 or 10 mg/bid or placebo (or adalimumab 40 mg/sc combined with a csDMARD instead of placebo in OPAL Broaden) in both trials. The efficacy of tofacitinib over placebo was evaluated with ACR20, ACR50, ACR70, HAQ-DI and PASI75. After three months, tofacitinib 5 mg/bid recipients achieved statistically significant ACR20 or ACR50 and HAQ-DI

scores than placebo in both trials, and in the OPAL Broaden study, significantly more patients treated with 5 mg/bid tofacitinib achieved PASI75 score than placebo. After 12 months, minimal disease activity was attained in 37% of tofacitinib 5 mg recipients. A minimal progression in radiography was reported in the OPAL Broaden trial, and more than 90% of patients showed non-progression criteria [22]. All reviewed studies reported favorable safety and efficacy profiles of oral tofacitinib and ruxolitinib.

Atopic Dermatitis

Atopic dermatitis is the most common chronic inflammatory skin disease with 3% – 10% prevalence in adults and 15% – 25% in children. Moderate-to-severe AD can alter the health-related quality of life (HRQoL) because of sleep disturbance, purities and comorbid mental conditions. Multiple inflammatory pathways and cytokines are involved in the pathogenesis of AD, and they can be considered as therapeutic targets [15,23].

Tsai et al conducted a meta-analysis on 15 RCTs and reviewed the efficacy and safety of JAKi in treating AD. Among 4,367 participants, 69 patients received topical tofacitinib 2% bid for 4 weeks, and 307 patients received topical ruxolitinib 0.15%, 0.5%, or 1.5% once daily, or 1.5% bid for 8 weeks. In the tofacitinib study, efficacy was evaluated by Investigator Global Assessment (IGA), Eczema Area and Severity Index (EASI-75%) and Body Surface Area (BSA) response. There were statistically significant higher rates of achievement to IGA, EASI-75%, and BSA responses in the treatment group compared to the control group. In assessing topical ruxolitinib among 307 patients, efficacy was evaluated by pruritus numerical rating scale (pruritus-NRS) response. Participants in the treatment group disclosed statistically greater rates of achieving pruritus-NRS response than placebo recipients. Additionally, safety was reported with Treatment-Emergent Adverse Events (TEAEs), showing a higher rate of AEs in the treatment groups that was directly related to the length of treatment (24). Further, it is suggested that topical JAKi are rational modalities in treating refractory AD; however, more clinical trials are required to evaluate the long-term safety.

Vitiligo

Vitiligo is an autoimmune skin disease with acquired loss of function in epidermal melanocytes, resulting in depigmented white patches of skin. The unregulated activity of T-helper1 and high levels of IFN- γ , IL-9 and IL-10 seem to be the leading cause of autoimmunity in vitiligo, and treatments aiming to lower the levels of ILs seem to be rationale [25,26].

Phan et al meta-analyzed data from nine case reports and case series to assess the pooled results about the efficacy and safety of JAKi in the treatment of vitiligo. Twenty-three

patients received oral tofacitinib 5 – 10 mg/bid for 12 – 40 weeks; 11 patients received topical tofacitinib 2% bid + UVB phototherapy for 12 weeks, 21 patients received topical ruxolitinib 1.5% bid for 12 – 38 weeks (in one study UVB phototherapy was also added), and one patient received oral ruxolitinib 20 mg/bid for 20 weeks. Efficacy was assessed with Vitiligo Area and Severity Index (VASI) and facial Vitiligo Area and Severity Index (fVASI). Overall effectiveness in the JAKi-alone recipients was reported as 57.8% good response, 22.2% partial and 20% none or minimal response. Moreover, the response to the treatment with concurrent UVB phototherapy was statistically higher than JAKi alone ($P < 0.001$). The improvement turned more significant (fVASI reduction) in facial vitiligo than other body sites ($P < 0.001$) when the studies were sub-grouped based on specific body areas. No significant difference was observed between different routes of JAKi administration ($P = 0.1$). AEs were erythema, transient acne, hyperpigmentation, transient hyperlipidemia, URTIs, weight gain and joint pain [27].

In a case report, Komnitski et al presented a 40-year-old lady with vitiligo and rheumatoid arthritis receiving 5 mg oral tofacitinib twice daily. After 2 years of the treatment without being sun-exposed, complete re-pigmentation of the frontal and peri-labial were observed. Further, partial improvement in the back of the neck and upper chest were also noted. No AEs were reported during the treatment in this case [28].

Lichen Planus

Lichen planus is a chronic inflammatory disorder that can involve derma, mucous, nail and hair follicles. The etiology of LP seems to be autoimmune with the incidence rate of 2% – 3% [30]. The overactivation of CD8+ T-call lymphocytes and dysregulation of CD4+ T-cells have been observed to play a major role in the pathogenesis of LP [30].

Damsky et al 2020 evaluated the benefit of oral tofacitinib in a case series of three patients with erosive lichen planus (ELP). Treatment with oral tofacitinib 5 mg/bid was initiated for all patients. Additional therapy with methotrexate and prednisolone was added to the therapeutic regimen of patient #1 due to the refractory course of his condition. All patients showed dramatic improvements and complete or near-complete remission while they were on tofacitinib. Discontinuation of tofacitinib in patient #1 resulted in ELP relapse even when he continued methotrexate and prednisolone. Re-initiation of tofacitinib 5 mg/bid resulted again in improvement in patient #1. Tofacitinib was tolerated well with no reported AEs in any of the cases [31].

Another case series by Yang et al reported the effectiveness of oral tofacitinib in ten patients with refractory lichen planopilaris (LPP). Treatment with tofacitinib 5 mg/bid for 8 patients and 5 mg/tds for the other 2 patients,

with more severe disease, was commenced and continued for 2 – 19 months. Disease activity assessed by LPP activity index (LPPAI), and showed statistically significant improvement compared to pre-treatment ($P = 0.0014$). One patient reported hair loss upon treatment discontinuation (due to weight gain), which stabilized when medication was re-started with a 5 mg/bid dosage [32]. A significant efficacy and low AEs were reported in the reviewed case series. Large-scale and long-term studies are required to assess the safety and efficacy of the treatment.

Hidradenitis Suppurativa

Hidradenitis suppurativa is a chronic inflammatory disorder in 1% of general population [33,34]. Pathogenesis of HS starts with cutaneous changes around hair follicles and dysregulation of innate and adaptive immunity: elevated levels of ILs following the overactivity of T-helpers, ultimately affect neutrophils, macrophages and plasma cells. These changes result in a vicious cycle of inflammation, pain, purulence, tissue destruction, and disfiguring scars [33-36]. JAKi suppress the impacts of ILs, and thus they can be a potential treatment for HS; however, limited studies aim to prove the benefit of JAKi in treating HS.

Savage et al reported two cases of HS treating with oral tofacitinib 5 mg/bid: a patient treated for one year and the other patient for three years. Both patients showed favorable results: patient #1 was pain and drainage free after 11 months. Upon discontinuation at 12 months, the modest disease activity was observed, and tofacitinib re-treatment directed the disease to full remission. Patient #2 experienced gradual remission over 3 years of treatment. At this time, localized herpes zoster infection was reported which was controlled with intravenous valacyclovir. No other AEs were reported in either of the two patients [35].

Pyoderma Gangrenosum

Pyoderma gangrenosum is a rare, ulcerative and painful dermatological condition with a multifactorial pathogenesis. Diagnosis of PG is clinical after excluding other causes ie infection, neoplasia, thrombophilia, and other inflammatory conditions. PG often is related to other systemic inflammatory conditions [37-40]. Pathophysiology of PG is not entirely known; however, it represents dysregulation of the innate and adaptive immune systems: neutrophil dysfunction, JAK2 mutation, overexpression of integrin and dysregulation of integrin signaling, and overproduction of ILs seems to be involved in the course of PG [41].

There are few studies about the efficacy of JAKi in treating PG; however, few case reports show potential benefits that need further large-scale RCTs. In a case report, Choi et al presented a patient with a history of cocaine abuse and 10-month PG lesions refractory to other forms of treatment,

including adalimumab, tacrolimus, prednisolone, and rituximab. Treatment was transitioned to oral tofacitinib 5 mg/bid: significant improvement was observed after two weeks, and 95% improvement and sustained remission were reported at three months post-treatment [42].

Another case report was conducted by Kochar et al presenting three patients with refractory PG. The first two patients were treated with 5 mg of tofacitinib twice daily, and no signs of disease activity and AEs were reported after 12 months. The third patient commenced on tofacitinib 5 mg/bid and concomitant steroid, and his PG lesions were improved but not healed entirely within a month. Then steroid was stopped, and tofacitinib up-titrated to 10 mg/bid and improvement continued [43]. Reviewed studies indicated the effectiveness of oral tofacitinib in the treatment of PG; however, more studies with larger scales are needed to assess the accuracy of this allegation.

Conclusions

Tofacitinib and ruxolitinib showed potential efficacy in the treatment of several autoimmune disorders. Based on a thorough review of the literature, it is concluded that both medications have acceptable safety profiles; however, physicians are recommended to outweigh the risks and benefits of the treatment for each specific condition. Further, there are not enough data and studies about the benefit and safety of tofacitinib and ruxolitinib in treating disorders such as HS, PG, and LP. We predict that JAKi will be utilized more broadly in treating autoimmune disorders, and future reviews can be a paradigm guideline helping clinicians to treat their patients.

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