JAK-STAT pathway and JAK inhibitors: a primer for dermatologists

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Background: All cellular events depend upon the DNA synthesis and gene expression involving complex interplay between ligands such as interleukins and interferons, with various cell membrane receptors. These ligand-receptors interactions transmit signals within the cell via numerous signal transduction pathways to affect gene expression. Janus kinase/signal transducer and activator of transcription pathway (JAK-STAT) are one of these pathways involved in the pathogenesis of various inflammatory and immunologic diseases. The therapeutic inhibition of this pathway has yielded promising results in many cutaneous and systemic disorders. It should be noted that, there are 4 JAK proteins and 7 STAT proteins. Currently, the first and second generations of JAK inhibitors are used for different indications, while more selective and pan-JAK inhibitors are under research.

Methods: we searched PubMed, Scopus, Cochrane library and Embase as search engines. The terms used to find the useful and appropriate articles were, "JAK-STAT pathway, janus kinase inhibitors and JAK-STAT inhibitors in dermatology".

Results: This article has summarized the different components of the JAK-STAT pathway, their regulation, classification of JAK inhibitors, and their adverse effects.

Conclusion: Based on the encouraging results of many ongoing clinical trials, their indications have been extended to various autoimmune dermatologic conditions in recent years.

Keywords: janus kinase, signal transduction, transcription pathway, STAT

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INTRODUCTION

Few non-polar molecules such as estrogens, testosterone and other steroid hormones are able to diffuse through the cell membranes and once inside the cell, these molecules can bind with proteins interacting directly with DNA and modulating gene transcription. However, most signal molecules are polar and too large to pass through the membrane, and they rely on various signal transduction pathways. The presence of a physiochemical signal is recognized by cell membrane receptors initiating a series of molecular events inside the cell, thereby resulting in various cellular responses such as changes in enzyme activity, gene expression, or ion-channel activity. This whole process is known as signal transduction. The Janus kinase (JAK)/ signal transducer and activator of transcription (STAT) pathway are one of the several signal transduction pathways, crucial for the biological response of various metabolically relevant hormones and cytokines, including growth hormone, leptin, erythropoietin, IL-4, IL-6 and IFN-γ [1]. JAK activation stimulates cell proliferation, differentiation, cell migration and apoptosis. These cellular events are critical to various biological responses such

as hematopoiesis, immunity, mammary gland development and lactation, adipogenesis, sexually dimorphic growth and other processes [2].

MATERIAL AND METHODS

To collect the data and information for this review, we searched PubMed, Scopus, Cochrane library and Embase as search engines. The terms used to find the useful and appropriate articles were, "JAK-STAT pathway, janus kinase inhibitors and JAK-STAT inhibitors in dermatology".

RESULTS

JAK- STAT Pathway [2,3]

The Actors

There are three main players in this pathway: Cell membrane receptor, Janus kinase (JAK) and Signal transducer, and activator of transcription (STAT) proteins. In mammals, 4 JAKs (JAK1, JAK2, JAK3, TYK2) and 7 STATs (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6) are employed by more than 50 cytokines and growth factors.

1. **Cell membrane receptor:** Three main families of receptors have been identified to act through the JAK- STAT pathway. The receptors (PTK receptors) for epidermal growth factor (EGF), platelet-derived growth factor (PDGF), colony stimulating factor 1 (CSF- I), hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), and insulin have an intrinsic protein tyrosine kinase (PTK) domain and can activate STATs themselves. Another large heterogeneous group of receptors, non-PTK receptors, binds with different cytokines. Another set of receptors, G-protein-coupled receptors/ seven pass transmembrane receptors, has been found to perform its biological functions through the JAK-STAT pathway.
2. **Janus kinases (JAK):** JAKs are cytoplasmic proteins of tyrosine kinase family. Seven JAK homology (JH 1-7) regions have been identified with tyrosine kinase domain (JH1) at the carboxyl (C)-terminus. A pseudokinase domain (JH2) is believed to play a role in maintaining JAK in its basal inactivated state. The F band 4.1, ezrin, radixin, moesin (FERM) homology domain (JH4-7) at the amino (N)-terminus is responsible for binding with the receptor's cytoplasmic domain. JH3 and JH4 are SH-2 domains having a structural role.
3. **STAT proteins** - In mammals, there are 7 STAT proteins. The amino-terminus of protein is involved in oligomerization of STAT dimers. Each STAT protein has 7 conserved domains: an N-terminal domain (NT), a coiled-coil domain (CC), a central DNA-binding domain (DBD), a linker region, an Src homology 2 (SH2) domain, a single conserved tyrosine residue, and a C-terminal transactivation domain (TAD). Inactivated non-phosphorylated STATs exist as anti-parallel dimers continuously shuttling between the cytoplasm and nucleus. Once membrane receptor binds with ligand, the STATs are localized to the receptor zone through interaction of its SH2 domain with the phosphotyrosine residues of the receptor. JAK activates STAT proteins by phosphorylation. Active STATs in a parallel dimer form stabilized by interactions of reciprocal SH2 domains and phosphotyrosine residues, disengages from the receptor and translocates to the nucleus. STAT1, 3, 4, 5 and 6 form homodimers. STAT2 mostly forms a heterodimer with STAT1. The tyrosine residue near transactivation domain also becomes phosphorylated, thereby enhancing transcriptional activity of STAT proteins.

The Show

The binding of ligand with a cell membrane receptor causes the receptor to dimerize and becomes phophorylated by JAKs. Dimerized receptors bring cytoplasmic domains of JAKs close to each other, enabling them to become auto- and/or trans-phosphorylated and thus activated. Meanwhile, STATs (shuttling between cytoplasm and nucleus) becomes localized to site of action through phosphorylated receptor. Activated JAKs phosphorylate STATs, causing spatial reorganization of the anti-parallel dimer complex, to create an active, parallel dimer form. Active STATs in a dimer form disengages from receptor and enters nucleus. Once inside the nucleus, STATs binds with specific regulatory sequences of DNA to influence (activate/ suppress) transcription of target genes and subsequent translation of proteins. The schematic diagram (Figure 1) summarizes the

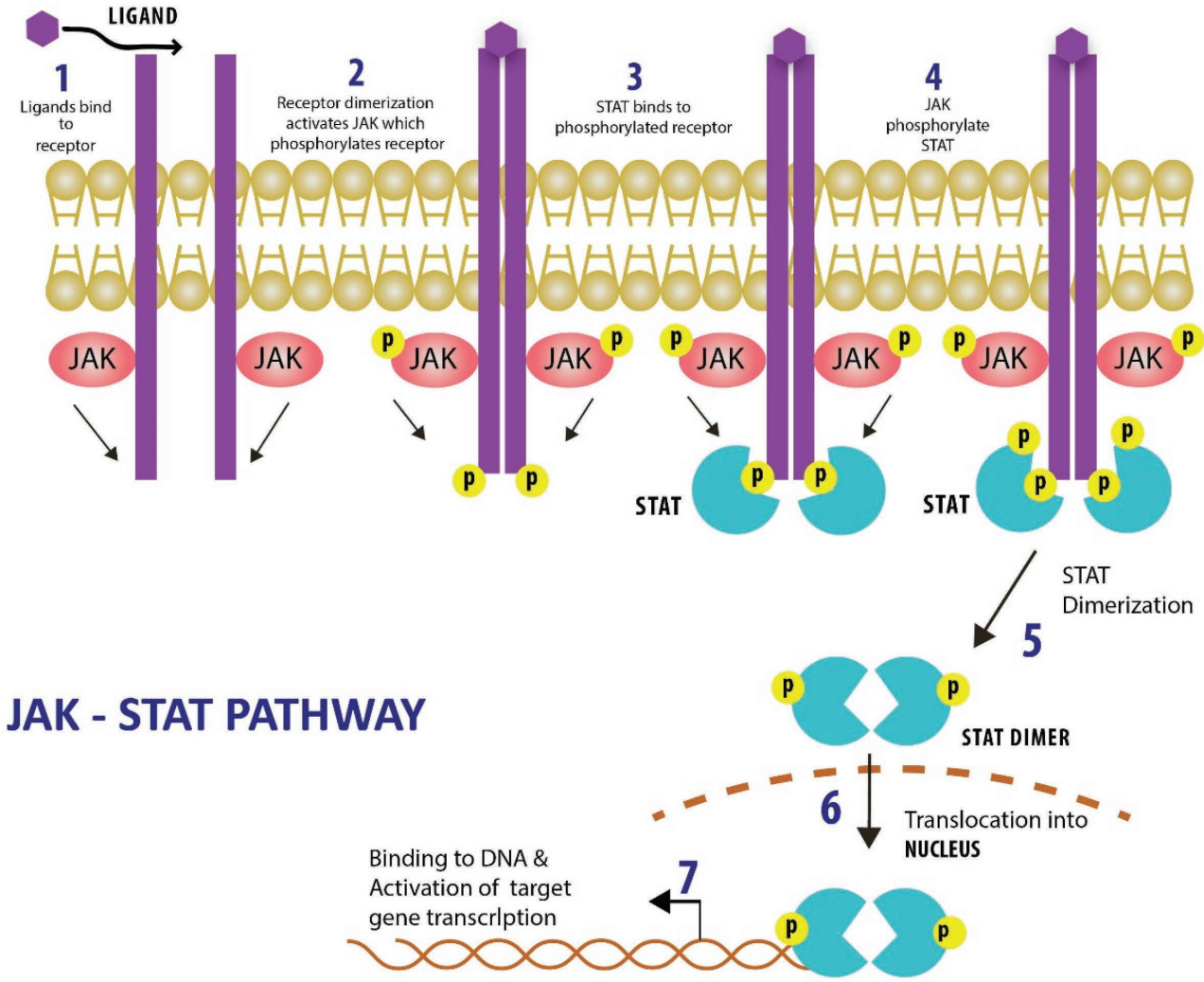

Figure 1. A simplified diagrammatic representation of the JAK-STAT pathway.

JAK- STAT pathway.

The Directors (regulators) of the Show

The regulators of the JAK- STAT pathway are as follows:

Positive Regulators

1. Signal-transducing adapter molecules (STAMs)- JAK1-JAK3 phosphorylates STAM 1 and STAM 2a, which in turn facilitate the transcriptional activation of specific target genes.
2. STAT-interacting protein (StIP)- StIP acts as a scaffold for the phosphorylation of STATs by JAKs.

Negative Regulators

1. Receptor internalization
2. Suppressors of cytokine signaling (SOCS)- Activated STATs induce the SOCS proteins binding with phosphorylated JAKs and their receptors to turn off the pathway.
3. Protein inhibitors of activated stats (PIAS)- PIAS binds with activated STAT dimers and prevent them from binding with the DNA.
4. Protein tyrosine phosphatases (PTPs) - dephosphorylates membrane receptor and JAKs.

JAK Inhibitors

JAK-STAT pathway is crucial for cytokines, interleukins and growth factors to transmit signal

resulting in DNA synthesis and gene expression involved in pathogenesis of various inflammatory and immunologic diseases. Various inflammatory dermatoses are driven from soluble inflammatory mediators relying on JAK-STAT signaling, and there is increasing evidence that inhibition of this pathway using JAK inhibitors has the potential to play a significant role in management of skin inflammatory disorders.

The first generation of JAK inhibitors includes tofacitinib, ruxolitinib, baricitinib, and oclacitinib. At present, ruxolitinib, a JAK1/2 inhibitor was approved by the US-FDA for myelofibrosis and tofacitinib, a JAK1/3 inhibitor has been recently approved for rheumatoid arthritis. Baricitinib and oclacitinib are not yet FDA approved but are undergoing clinical trials for rheumatoid arthritis and atopic dermatitis in dogs, respectively. Table 1 summarizes the first and second generations of JAK inhibitors.

A new generation of JAK inhibitors, including both pan-JAK inhibitors (JAK1, JAK2, JAK3, and Tyk2) and selective JAK inhibitors (ie, JAK1 only or JAK3 only), is under development. In multiple studies, the use of topical JAK inhibitors is also explored in dermatological inflammatory disorders.

Dermatological Indications

Although JAK inhibitors have not been approved for use in any dermatological inflammatory and immune disorders, recently growing evidence has indicated promising outcomes in various clinical trials. To date, in dermatology, psoriasis has been the most widely studied indication for JAK inhibitors. The FDA has not yet approved tofacitinib for this indication. Other dermatological conditions such as alopecia areata, vitiligo, atopic dermatitis, and

Table 1. Classification of JAK inhibitors

Classification, signaling pathway and dermatological indications					
1st generation drugs (broadly acting)	**Targeted JAK**	**Dermatological indications**	**2nd generation investigational drugs (more selective)**	**Targeted JAK**	**Dermatological indications**
Tofacitinib	JAK 3/1 >> JAK 2	Phase 3: Psoriasis	Filgotinib (GLPG-0634)	JAK 1	Cutaneous LE (phase 2)
		Phase 2: Vitiligo STING-SAVI CAD Juvenile Dermatomyositis Palmoplantar pustulosis AA HES LE Atopic dermatitis EM			
Ruxolitinib	JAK 1/2	Phase 2: AA Vitiligo Psoriasis STING-SAVI Juvenile dermatomyositis LE Mastocytosis	Itacitinib	JAK 1>JAK 2	Psoriasis and chronic pruritus (phase 2) GVHD (phase 1)
Baricitinib	JAK 1/2	Phase 2: Atopic dermatitis Psoriasis SLE	Peficitinib (ASP-015K)	JAK 3/1 >> JAK 2	Psoriasis (phase 2)
Oclacitinib	JAK 1	Canine atopic dermatitis (FDA approved)	PF-04965842	JAK 1	Psoriasis (phase 2) Atopic dermatitis (phase 2)
			Lestaurtinib (CEP-701)	JAK 2	Psoriasis (phase 2)
			Upadacitinib (ABT-494)	JAK 1	Atopic dermatitis (phase 2)
			Solcitinib (GSK-2586184/ GLG-0778)	JAK 1	SLE (phase 2) Psoriasis (phase 2)

PAN: polyarteritis nodosa; GVHD: graft versus host disease; STING-SAVI: stimulator of interferon genes-associated vasculopathy with onset in infancy; HES: hypereosinophilic syndrome; LE: lupus erythematosus; CAD: chronic actinic dermatitis; AA: alopecia areata; EM: erythema multiforme.

nail dystrophy associated with alopecia areata have also shown favorable outcomes with JAK inhibitors in many clinical trials. There are some case reports showing the efficacy of tofacitinib in chronic actinic dermatitis, dermatomyositis, erythema multiforme, hypereosinophilic syndrome, lupus erythematosus, palmplanter pustulosis, graft versus host disease and polyarteritis nodosa.

Psoriasis

The pathogenesis of psoriasis involves various cytokines out of which IL-12 and IL-23 are the key mediators. IL-23 stimulates TH17 cells to produce IL-17 as another important pathogenic molecule in psoriasis. Blockade of IL-23 using tofacitinib indirectly results in a decrease in IL-17 [4]. Phase 3 randomized controlled trials (RCT) of tofacitinib 5mg and 10mg have demonstrated better improvement in PGA and PASI compared to placebo [5-7]. Histopatholohical evaluation of tofacitinib treated lesions showed reduced cytokines, lower numbers of DC and T cells, and decreased IL-23/Th17 activity [8]. Tofacitinib 10mg was found to be non-inferior to etanercept 50mg subcutaneously twice weekly in two RCTs [9,10]. Both the dosing regimen 5mg and 10mg had a similar safety profile. Obesity and prior biologic treatment result in poor outcomes.

Topical JAK inhibitors are explored in psoriasis. Tofacitinib 2% ointment, ruxolitinib 1% and 1.5% creams applied twice daily led to improvement in psoriasis lesions [11]. However, further trials are needed to establish efficacy of topical JAK inhibitors in psoriasis.

Atopic Dermatitis

The pathogenesis of atopic dermatitis (AD) is complex, but in part involves increased helper T cell type 2 (TH2) immunity driven from JAK-STAT signaling downstream of cytokines, such as IL-4, IL-5, and IL-13. Tofacitinib 5mg daily or twice daily had shown a 66.6% reduction in the severity scoring of AD Index and a 69.9% reduction in pruritus and sleep loss scores in patients with moderate to severe AD for whom all common treatments failed to treat them [12].

In a phase 2 study comparing topical tofacitinib 2% with vehicle, a more significant reduction in the area and severity of eczema was shown in the tofacitinib group in comparison to placebo [13].

Alopecia Areata (AA)

In AA, JAK-STAT dependent cytokines, including IFN-g and IL-15, drive proliferation and activation of autoreactive CD8+ T cells, suggesting that JAK inhibition may be an effective treatment. There are some trials of JAK inhibitors reporting either improvement in SALT score or some hair growth in various types of alopecia areata.

Table 2. Adverse effects of JAK inhibitors

	Adverse effects	Immunopathological basis
I.	Opportunistic infections: [28]	
	Bacterial infections – urinary tract infection, bronchitis, pulmonary tuberculosis	Suppression of γc cytokine mediated JAK 1/3 signaling
	Viral – Nasopharyngitis, non-disseminated herpes zoster, disseminated molluscum contagiosum, acute gastroenteritis, cytomegalovirus and BK virus infection	Decreased antiviral actions of IL-15 dependent NK cells and IFNs due to JAK1/3 inhibition
	Fungal – candidiasis, pneumocystis pneumonia and cryptococcosis	Reduced action of IFN-γ, IL-12 and IL-6
II.	Cytopenia: anemia, leucopenia and thrombocytopenia	Inhibition of GM-CSF, EPO and TPO mediated JAK 2 signalling
III.	Hypercholesterolemia: Elevation of LDL, triglyceride and total cholesterol levels in serum	Blockade of IL-6 mediated upregulation of ABC-A1 and cholesterol efflux to apolipoprotein A1
IV.	Risk of malignancies: lymphoproliferative disorders, cutaneous T-cell lymphoma, non-melanoma skin cancers	Suppression of IFNs mediated tumor surveillance
V.	Drug reactions: drug reaction with eosinophilia and systemic symptoms (DRESS) [29]	Idiosyncratic
VI.	Impaired response to vaccination [30]	Impaired IFNs driven T-cell and B-cell development and reduced IL-6 and IL-21 mediated B-cell differentiation into antibody-producing cells
VII.	Elevation of serum creatinine and transaminases level	Not clearly understood

Tofacitinib has been found efficacious in patients with AA, alopecia totalis (AT) and alopecia universalis (AU) with >50% improvement in the SALT score in 58% of patients and >90% improvement in 20% of patients, while 77% of patients reported some hair growth [14]. In another study of adolescents (12-17 years old) with severe AA, AT, and AU, after a mean of 6.5 months of treatment with tofacitinib reported a 93% median change in SALT score from the baseline [15]. Furthermore, tofacitinib 5 mg twice daily for 5-6 months in 3 patients with AU and nail dystrophy resulted in remission of nail dystrophy. As in AD, topical JAK inhibitors are under investigation in AA [16]. In one report, a patient treated with ruxolitinib 0.6% cream twice a day for 12 weeks to the eyebrows and scalp, showed complete eyebrow regrowth and partial scalp hair regrowth [17].

Vitiligo

Vitiligo might be susceptible to treatment with JAK inhibitors, since IFN-γ utilizes the JAK-STAT pathway to mediate targeted destruction of melanocytes by CD8+ T cells. Generalized vitiligo showed near complete repigmentation of affected areas of the face, forearms, and hands over 5 months of treatment with tofacitinib (5mg every other day for 3 weeks followed by 5 mg daily). Following treatment discontinuation, however, loss of repigmentation was observed [18]. The authors proposed that JAK1/JAK2 was involved in INF-γ signal transduction. They also indicated that the use of the JAK1/3 inhibitor blocked the INF-γ signaling and decreased C-X-C motif chemokine 10 (CXCL10) expression. The expression of CXCL10 in keratinocytes is induced by INF-γ, and it has been found to be an intermediate of depigmentation in vitiligo.

Adverse Effects

Data regarding safety of JAK inhibitors from trials of tofacitinib and ruxolitinib in rheumatoid arthritis and myelofibrosis, respectively, have shown that the risk of adverse effects like infections is similar to other targeted immunosuppressive therapies, and major adverse events were low (<1%), with a similar rate compared to all approved TNF inhibitors. All the reported side effects can be divided into two groups: cutaneous and non-cutaneous.

Cutaneous side effects*:* Herpes zoster, varicella, disseminated molluscum, herpes simplex, drug rash, DRESS syndrome and eruptive squamous cell carcinoma have been reported with tofacitinib.

Non-dermatological side effects*:* Upper respiratory tract infections, nasopharyngitis, gastrointestinal perforation, enterovaginal fistula, headache, distal symmetric polyneuropathy are some of the non dermatological side effects. No cases of reactivation of tuberculosis were found in a systematic review of 5 RCTs with tofacitinib [19]. Dose dependent cytopenias are another potential adverse effect of JAK 2 inhibitors, since signaling through JAK2 is mediated by erythropoietin, thrombopoietin, and granulocyte colony stimulating factor, accordingly cytopenias are more encountered with ruxolitinib than tofacitinib. With ruxolitinib, the most common infection was urinary tract infection. Another concern with JAK inhibitors is increased risk of malignancy. Some studies of tofacitinib in renal transplantation showed that 1% patients treated with tofacitinib developed the post-transplant lymphoroliferative disorder [20]. However, in these studies, tofacitinib was used in higher doses (10-30 mg) with other immunosuppressive agents, and no such adverse effect was reported in studies of tofacitinib in inflammatory disorders. Longer studies are necessary to determine the further drug safety. Table 1 summarizes adverse effects and their immunopathologic basis [21-23].

There are some screening tests, which should always be conducted before starting treatment and have to be repeated at some intervals. Table 3 presents a summary of the cases [24].

Future Directions

Considering the side effects and variable efficacy of different JAK inhibitors and the variable clinicopathological course of autoimmune inflammatory diseases, there is a justified need to compare the efficacy and safety profile of pan-JAK inhibitors and selective or second generation JAK inhibitors. In addition, advent of these drugs exposes the possibilities to target 3 other steps of JAK-STAT pathway: direct inhibition of phosphorylation of STAT proteins and cytokine receptors by JAK proteins; blocking SH2 domain of STAT proteins (mediating binding to phosphorylated cytokine

Table 3. Recommendations prior to and during treatment

Screening tests [31]
Pre-treatment:
● Complete blood count
● Renal and hepatic function
● Fasting serum lipid profile
● HBV, HCV, tuberculosis and HIV
During treatment:
● Repeat all the tests (except HBV, HCV, HIV and tuberculosis) 1 month after initiation of treatment and then every 3 months thereafter.
● Screening for tuberculosis should be performed annually.
● In the case of severe renal and/or hepatic impairment or in the setting of concomitant enzyme inhibitors CYP3A4 and CYP2C9 inhibitors like azoles.

HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus

receptor before dimerization); and DNA binding of STAT [25]. Certainly, considerable investigational effort and various research trials are required to bring such molecules to clinical use for dermatologists and clinicians.

CONCLUSION

Over the past decade, bar has been raised with the addition of biologics and biosimilars in the treatment of various autoimmune and rheumatic diseases. Advancement in the molecular medicine has made it plausible to have therapeutic implications of the JAK-STAT pathway in the form of JAK inhibitors in many haematological disorders and malignancies. Based on the encouraging results of many ongoing clinical trials, its indications have been extended to various autoimmune dermatologic conditions in recent years. In this regard, many problems such as their high cost, known and predictable side effects, in-vivo efficacy, bioavailability and selectivity limiting their use in the current scenario, have to be obviated. To make the use of such an emerging class of drugs feasible in dermatology, a large number of randomized clinical trials and meta-analyses are needed.

Conflict of Interest: None declared.

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