Review Article

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Tofacitinib's Role in Efficacy and New Developments in Dermatology (TREND)

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Abstract

Despite many scientific advancements, we haven't found satisfactory treatment for many dermatomes. The disFig.ment caused by these conditions is a source of distress. Pathophysiology of certain dermatomes roots from common pathophysiology. Though lots of medical treatments are available, however, they provide transient relief. Symptoms often re-appear after sometime.The conditions have a negative effect on overall quality of life of the patients leading to anxiety and depression in some cases. Usually these conditions take a long time to be asymptomatic only to relapse later. Janus kinase inhibitors (Jaknibs) are novel medications approved to be used in rheumatological conditions. Increasing evidences have shown their efficacy in many dermatological conditions such as psoriasis, vitiligo, atopic dermatitis, alopecia areata and a few others. Tofacitinib was first approved in 2012 by USFDA for the management of rheumatoid arthritis. Tofacitinib inhibits JAK1 and JAK3, reducing the signaling of pro-inflammatory cytokines. This inhibition affects various immune processes, which is beneficial in treating inflammatory and autoimmune conditions, including those affecting the skin.The drug is being accepted in dermatological conditions. In many other dermatoses, JAK inhibitors carry a promise in management. Cutaneous graft-versus-host disease, erythema multiforme, dermatomyositis, chronic actinic dermatitis, and lupus and hypereosinophilic syndrome are few of such conditions. In the present review, we discuss the literature and evidence of the use of tofacitinib in dermatological conditions.

Keywords: Tofacitinib; JAK-STAT; JAK inhibitor; Alopecia areata; Atopic dermatitis; Psoriasis; Vitiligo.

INTRODUCTION

Despite advances in management of dermatology, there are still many conditions which are often difficult to manage. With current medications there are transient relief, however, after sometime the symptoms re-appear sooner or later. Whereas the conditions have overall impact on physical health, most dermatological conditions are cosmetically unacceptable and have a grave impact of self-esteem and quality of life. Many of these conditions

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such as Atopic Dermatitis (AD), Alopecia Areata (AA), vitiligo, and psoriasis are autoimmune in nature. No surprise some medicines having immunomodulatory functions, have been found to be effective in these conditions.

Janus kinase inhibitors (Jakinib) block tyrosine kinases of the Janus family. Janus kinase-signal transducer and activator of transcription (JAK/ STAT) is an intracellular pathway. It regulates downstream signaling of many pro-inflammatory pathways. Jakinibs have proven their high efficacy in management of various inflammatory conditions such as rheumatoid arthritis (RA) and ulcerative colitis (UC). Looking at their mechanism and efficacy in diverse conditions, they carry a promising role in dermatological inflammatory conditions as well.

There are lots of advantages with Jakinibs which make them an appealing choice as a targeted therapy over biologics. Few among them inhibition of signaling from multiple cytokines, oral and topical routes and unreported potential of generating neutralizing antibodies.

Tofacitinib is an oral Janus kinase (JAK) inhibitor. Initially it was approved for the treatment of rheumatoid arthritis, now its use has expanded into dermatology also, owing to its ability to modulate the immune response effectively. It is emerging as among treatment of choice in numerous dermatological conditions. The objective of this article is to explore role of tofacitinib in management of dermatological inflammatory conditions. In this article, we review the approved and emerging use of tofacitinib in psoriasis, vitiligo, atopic dermatitis and alopecia areata.

Pharmacology of Tofacitinib

Tofacitinib is amongst first generation JAK inhibitors; other being ruxolitinib, baricitinib, and oclacitinib. Tofacitinib is the first FDA-approved JAK inhibitor for treatment of an autoimmune disease.

Tofacitinib inhibits JAK1 and JAK3, reducing the signaling of pro-inflammatory cytokines. This inhibition affects various immune processes, which is beneficial in treating inflammatory and autoimmune conditions, including those affecting the skin.

There is increasing body of evidence showing that JAK inhibitors are effective not only in management of psoriasis, but also other inflammatory dermatologic conditions as well. Many dermatologically relevant cytokines such as IFN-α/β, IFN-γ, IL-2 receptor common γ-chain interleukins (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21), and IL-5, IL-6, IL-12, IL-13, and IL-23 act through JAK-STAT pathway. Also, JAK inhibitors can indirectly subdue action of other cytokines.[7]

Clinical Efficacy of Tofacitinib in Dermatological Conditions

Tofacitinib was first approved in 2012 by USFDA (United States Food and Drug Administration). It was approved for treatment of moderate to severe rheumatoid arthritis. Over last many years the molecule has been found to be effective in not only rheumatoid arthritis, but also in many dermatological conditions. It is a JAK 1/3 inhibitor. Research has shown role of JAK pathway in etio-pathogenesis of many dermatomes. This seems to be possible mechanism of its efficacy in psoriasis, alopecia areata, vitiligo and other conditions. We are getting more and more information on tofacitinib's role in these conditions as evidences are being generated.

Whereas alopecia areata and vitiligo look entirely different dermatological conditions with separate sets of symptoms; a striking similarity in their genetic risk factors has been observed. Also, the conditions are found within families and/ or individual patients as well. The common pathologies among AA and vitiligo include the involvement of plasmacytoid dendritic cells (and interferon-α (IFN- α) signaling pathways) and cytotoxic CD8+ T lymphocytes (and activated IFN-γ signaling pathways). Blood chemokine C-X-C motif ligand 9 (CXCL9) and CXCL10 are elevated in both diseases.All of the above factors suggest reason why tofacitinib has been found to be effective in both conditions.

Psoriasis

Psoriasis is a chronic, immune-mediated disease characterized by rapid growth of skin cells, resulting in scaling and inflammation. Clinical trials have demonstrated that tofacitinib is effective in reducing the severity of plaque psoriasis.

Phase 3 randomised clinical trials have established the efficacy of tofacitinib in moderate to severe plaque psoriasis. PASI 75 response at 12 weeks was 39.5% with 5mg bd dosage, whereas it was 63.6% with 10mg bd. Also, tofacitinib 10mg was found to be non-inferior to twice weekly sc etanercept 50mg therapy. There was no significant difference in adverse effects with 5mg & 10mg regimen. Other trials have produced similar results.[7]

Atopic Dermatitis

Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin condition that typically affects the face, neck, arms, and legs but usually spares the groin and axillary regions. AD usually starts in early infancy, but also affects a substantial number of adults.Moisturizers and topical steroids are used as a first line therapy for AD. However, often these are not sufficient. Tofacitinib has shown promising response to Atopic dermatitis as well. Itching and skin lesions have reduced in AD patients in studies with use of tofacitinib. AD has a complicated pathology, however, it has been proven that at least a part of AD is because Th2 immunity increase due to JAK-STAT signaling downstream of cytokines such as IL-4, IL-5, and IL-13.

In a clinical trial, improvement in six patients with moderate to severe AD with failed common treatments, was noted with oral tofacitinib. There was reduction of 66.6% in the Severity Scoring of AD Index (SCORAD) and a 69.9% in pruritus and sleep loss scores with tofacitinib 5mg daily or 10mg daily in divided doses. Though there was no control group in this study, still the improvement in patients with failed treatment should be considered a positive sign.

Alopecia Areata

Alopecia Areata (AA) is another dermatological condition that impacts the patient psychologically. There are typical non-scarring patch/es of hair loss with characteristic exclamation mark hair. The prevalence ranges from 0.1% to 0.2% across world. AA is commonly associated with other autoimmune conditions ranging from autoimmune thyroid diseases, systemic lupus erythematosus, vitiligo,and atopic dermatitis.[11]

Some trials have shown promising results with tofacitinib in AA. 66 patients were enrolled in a study and given 5mg tofacitinib for 3 months. Patients were diagnosed with severe AA, alopecia total is (AT), or Alopecia Universal is (AU). Approximately two third of these patients had improved hair regrowth. Also, there was >50% improvement in their Severity of Alopecia Tool (SALT) score in 32% of these patients.

Tofacitinib has treated successfully severe AA, AT and AU for a period up to 18 months. A trial was conducted in 65 adult patients with AT or AU with duration of less than or equal to 10 years or severe AA. 77% of the total patients achieved some hair growth with 58% achieving more than 50% improvement. 20% patients achieved >90% improvement in SALT score. In patients with more than 10 years of duration, hair growth was not much.93% median change was observed in SALT score after average 6.5 months treatment with tofacitinib in a case series with adolescents suffering from AA, AT and AU. There were no control groups in above mentioned studies, however, the results are encouraging, as in long standing conditions with severe symptoms, there are little chances of spontaneous resolution of symptoms.

Vitiligo

Vitiligo a disfiguring disease, is result of melanocyte loss. As it progresses, it produces negative impact on personality leading to anxiety and depression in some cases. Aim of treating vitiligo is to halt its spread and increase repigmentation of areas affected. Narrow band ultraviolet B phototherapy with topical medications are primary treatment. However, these measures fail to control its progress. Role of corticosteroid has been found to be effective in certain cases, however, their usage is associated with major unacceptable adverse effects.

A retrospective study was done in 25 patients who were refractory to systemic steroid treatment to analyze effect of tofacitinib in these patients. Disease progression was halted in 64% (total 16) out of these 25 patients. Progression of the disease stopped within a month in around half among these 16 patients. Repigmentation was observed in total 40% (10) of these patients, degree varying in all patients.

In a retrospective case series 10 patients were prescribed tofacitinib 510 mg daily/twice daily for 315 months. The outcome measures were a decrease in BSA of depigmentation. A mean decrease of 5.4% BSA involvement with vitiligo was observed in 5 of 10 patients, only in sunexposed or NBUVB phototherapy treated areas. The most common AEs noted were URTI, weight gain, arthralgia, and mild elevations of lipid levels. No serious AE was reported in this case series.

In a case report of 2 patients with longstanding vitiligo with significant facial involvement tofacitinib 5 mg BD was given with lowdose NBUVB 23 times weekly. The duration of therapy was 36 months. Arapid and nearly complete repigmentation of face after 36 months was reported in this case report with no major AE.

Safety and Tolerability

As with other medications having immunomodulatory actions, JAK inhibitors are associated with higher risk of infections &

malignancies. Most common adverse effects associated with oral tofacitinib are upper respiratory tract infections, diarrhea, headache and viral infection reactivations like herpes zoster. High dose with concomitant immunomodulators may pose increased risk of disseminated disease and other serious infection. One needs to be cautious and increased monitoring is required.

There have been reports of reactivation of latent tuberculosis infections (LTBI) in patients on tofacitinib. India is an endemic country for TB, so one needs to be cautious while prescribing these medicines and before starting the treatment proper screening should be done. In patients with LTBI, isoniazid (INH) prophylaxis can protect from developing active infection. Tolerability and safety profile has been found to be consistent in dermatological conditions with its use in other indications. Most long term safety data suggests manageable safety profile with medical supervision.

Impact on Quality of Life

Despite reasonably good advancement in management of dermatoses, there are still unmet needs in these conditions. Usually these conditions take a long time to be asymptomatic only to relapse later. The disfiguring caused are source of distress and anxiety, especially in younger age group patients. With increasing evidences of tofacitinib in many of these conditions, the dermatologists have one more arrow in their quiver. The rapid and sustainable efficacy is equally desired by the physicians and patients. Tofacitinib seems, at least partially, meeting these need of hour. Patient satisfaction surveys highlight the drug's effectiveness in reducing discomfort and improving overall life quality. Rapid improvement in symptoms lead to better physical, cosmetic and psychological wellbeing. There are evidences of reduction of discomfort and improvement in overall quality of life.

Most of the safety data available with tofacitinib has been derived from large trials done in RA and psoriasis patients. Overall risk of infections and mortality are comparable with other immunosuppressive therapies. Increased risk of varicella zoster reactivation has been observed with tofacitinib. Usually it is limited to localized disease. There are reports of vaccination having reduced response, wherever possible, immunizations should be done before starting treatment. There has been hypothesis of higher risk of malignancy. Few studies have shown development of post-transplant lymphoproliferative disorder in ~1% of renal transplantation patients on tofacitinib. It should be noted that these patients were on a higher dose of tofacitinib and patients were concomitantly on other immunosuppressive agents. In other patients (RA and psoriasis etc) increased risk of cancers has not been noted.[7]

Dosage and Administration

Tofacitinib is typically administered orally, with dosages varying based on the condition being treated. For psoriasis and atopic dermatitis, common dosages range from 5 to 10 mg twice daily. Adjustments may be necessary for patients with renal or hepatic impairments and for those experiencing adverse effects.

CONCLUSION

Tofacitinib represents a significant advancement in the treatment of dermatological conditions. Its efficacy in managing symptoms, coupled with a relatively manageable safety profile, makes it a valuable addition to dermatology. Ongoing research and real-world data will continue to refine its use, ensuring that it remains a key option for patients with chronic and severe skin conditions.

Owing to common aetiopathogenesis in many autoimmune conditions, JAK inhibitors are proving to be efficacious agents not only in rheumatological conditions but also in several dermatological conditions as well. Tofacitinib is the first JAK inhibitor approved more than a decade ago in rheumatoid arthritis. Post its marketing, the JAK inhibitor has been proven highly efficacious in multiple conditions. The evidence is ever increasing in dermatology since its introduction. Psoriasis, vitiligo, atopic dermatitis, and alopecia areata are some of the major conditions which have a plethora of evidence of efficacy with tofacitinib. The agent has been used safely in these conditions. The patients are being benefitted with better outcomes and quality of life. Clinicians have an added armamentarium against these not so easy to treat conditions. More researches are currently underway for expansion of its usage in other conditions.

There are many more dermatologic diseases where JAK inhibitors carry a promise in management. Few of such conditions are cutaneous graft-versus-host disease, erythema multiforme, dermatomyositis, chronic actinic dermatitis, and lupus and hypereosinophilic syndrome among others.

REFERENCES

1. Khandpur, S.; Sharma, V.K.; Sumanth, K. Topical immunomodulators in dermatology. Journal of Postgraduate Medicine 50(2):p 131-139, June 2004.
2. Shreberk-Hassidim R., Ramot Y., Zlotogorski A. Janus kinase inhibitors in dermatology: A systematic review. *J. Am Acad Dermatol* 2017; 76:745-753.
3. Samadi A., Ahmad Nasrollahi S., Hashemi A., Nassiri Kashani M., Firooz A. Janus kinase (JAK) inhibitors for the treatment of skin and hair disorders: A review of literature. *J. Dermatol Treat* 2017; 28:476-483.
4. Ghoreschi K., Gadina M. Jakpot! New small molecules in autoimmune and inflammatory diseases. *Exp Dermatol*2014;23:7-11.
5. Kyle Tegtmeyer, Jeffrey Zhao, Off-label studies on tofacitinib in dermatology: A review, Journal of Dermatological Treatment, DOI: 10.1080/09546634.2019.1673877
6. Fatemeh Zabihi, Mariam Cherri, Xiao Guo, Topical Delivery of Tofacitinib in Dermatology: The Promise of a Novel Therapeutic Class Using Biodegradable Dendritic Polyglycerol Sulfates Pharmaceuticals 2024, 17(1), 77; https://doi.org/10.3390/ph17010077
7. Ciechanowicz, P.; Rakowska, A.; Sikora, M.; Rudnicka, L. JAK-inhibitors in dermatology. Current evidence and future applications. J. Dermatol. Treat. 2019, 30, 648–658
8. Ghoreschi K., Jesson M.I., Li X., *et al*. Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). *J. Immunol*. 2011; 186(7):4234–4243.
9. Schwartz D.M., Bonelli M., Gadina M., O'Shea J.J. Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases. *Nat Rev Rheumatol*. 2016; 12(1):25–36.
10. Riese R.J., Krishnaswami S., Kremer J. Inhibition of JAK kinases in patients with rheumatoid arthritis: scientific rationale and clinical outcomes. Best Pract Res Clin Rheumatol. 2010;24(4): 513–526.
11. Hiroki L. Yamaguchi, Yuji Yamaguchi and Elena Peeva *et al*. Pathogenesis of Alopecia Areata and Vitiligo: Commonalities and Differences. *Int. J. Mol. Sci.* 2024, 25, 4409.
12. Bachelez H., van de Kerkhof P.C., Strohal R., *et al*. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. *Lancet*. 2015; 386(9993):552–561.
13. Papp K.A., Menter M.A., Abe M., *et al*. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials. *Br J. Dermatol*. 2015; 173(4):949–961.
14. Leung D.Y., Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: shifting paradigms in treatment approaches. *J. Allergy Clin Immunol*. 2014; 134(4):769–779.
15. Islam N., Leung P.S., Huntley A.C., Gershwin ME. The autoimmune basis of alopecia areata: A comprehensive review. *Autoimmun Rev*. 2015; 14(2):81–89.
16. Chu S.Y., Chen Y.J., Tseng W.C., *et al*. Comorbidity profiles among patients with alopecia areata: the importance of onset age, a nationwide population-based study. *J. Am Acad Dermatol.* 2011; 65(5):949–956.
17. Lee N.R., Kim B.K., Yoon N.Y., Lee S.Y., Ahn S.Y., Lee W.S. Differences in comorbidity profiles between early-onset and late-ons*et al*opecia areata patients: a retrospective study of 871 Korean patients. *Ann Dermatol.* 2014;26(6):722–726.
18. Huang K.P., Mullangi S., Guo Y., Qureshi A.A., Autoimmune QAA. Autoimmune, atopic, and mental health comorbid conditions associated with alopecia areata in the United States. *JAMA Dermatol*. 2013;149(7):789–794.
19. Kennedy Crispin M., Ko JM., Craiglow B.G., *et al*. Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata. *JCI Insight*. 2016; 1(15):e89776.
20. Liu L.Y., Craiglow B.G., Dai F., King B.A. Tofacitinib for the treatment of severe alopecia areata and variants: a study of 90 patients. *J Am Acad Dermatol*. 2016 in press.
21. Craiglow B.G., Liu L.Y., King B.A. Tofacitinib for the treatment of alopecia areata in adolescents. *J Am Acad Dermatol*. 2016 in press.
22. Khadeejeh AL-smadi, Mohammad Imran, Yousuf Mohammed, Vitiligo: A Review of Aetiology, Pathogenesis, Treatment, and Psychosocial Impact Cosmetics 2023, 10(3), 84
23. Xiu-kunSun, An-qiSheng, and Ai-eXu. Tofacitinib for the Treatment of Refractory Progressive Vitiligo: ARetrospective Case Series. *Dermatologic Therapy Volume* 2024, Article ID 9944826, 5 pages. https://doi.org/10.1155/2024/9944826
24. Liu L.Y., Strassner J.P., Refat M.A., Harris J.E., King B.A. Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. *J. Am Acad Dermatol* 2017; 77:675682.
25. Kim S.R., Heaton H., Liu L.Y., King B.A. Rapid repigmentation of vitiligo using tofacitinib plus lowdose, narrowband UVB phototherapy. *JAMA Dermatol* 2018; 154:370.
26. Welsch K., Holstein J., Laurence A., Ghoreschi K. Targeting JAK/STAT signalling in inflammatory skin diseases with small molecule inhibitors. *Eur J. Immunol* 2017; 47:1096-1107.
27. Sonthalia S., Aggarwal P. Oral tofacitinib: Contemporary appraisal of its role in dermatology. *Indian Dermatol Online J.* 2019;10:503-18.

28. Strober B.E., Gottlieb A.B., van de Kerkhof PCM, Puig L., Bachelez H., Chouela E., Imafuku S., Thaçi D., Tan H., Valdez H., Gupta P., Kaur M, Frajzyngier V., Wolk R. Benefit-risk profile of tofacitinib in patients with moderate-to-severe chronic plaque psoriasis: pooled analysis across six clinical trials. *Br J. Dermatol*. 2019 Jan; 180(1):67-75. doi: 10.1111/bjd.17149.
29. Damsky W., King B.A. JAK inhibitors in dermatology: The promise of a new drug class. *J. Am Acad Dermatol*. 2017 Apr; 76(4):736-744. doi: 10.1016/j.jaad.2016.12.005.
30. Busque S, Leventhal J., Brennan D.C., *et al*. Calcineurin-inhibitor-free immunosuppression based on the JAK inhibitor CP-690,550: a pilot study in de novo kidney allograft recipients. *Am J. Transplant*. 2009; 9(8):1936–1945.
31. Vincenti F., Tedesco Silva H., Busque S., *et al*. Randomized phase 2b trial of tofacitinib (CP-690,550) in de novo kidney transplant patients: efficacy, renal function and safety at 1 year. *Am J Transplant*. 2012; 12(9):2446–2456.
32. Vincenti F., Silva H.T., Busque S., *et al*. Evaluation of the effect of tofacitinib exposure on outcomes in kidney transplant patients. *Am J. Transplant*. 2015; 15(6):1644–1653.
33. William Damsky and Brett A. King. JAK inhibitors in dermatology: the promise of a new drug class. *Am Acad Dermatol*. 2017;76(4): 736–744. doi:10.1016/j.jaad.2016.12.005.