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A NARRATIVE REVIEW ON EVALUATING THE SAFETY OF JANUS KINASE (JAK) INHIBITORS IN DERMATOLOGICAL PRACTICE: A CLINICAL AND LABORATORY PERSPECTIVE.

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ABSTRACT
The introduction of Janus kinase (JAK) inhibitors has modernized the treatment of various dermatological conditions by targeting the JAK-STAT signaling pathway, essential in the pathogenesis of inflammatory and auto-immune diseases. Despite their therapeutic potential, concerns regarding their safety and tolerability necessitate a comprehensive review. To synthesize current knowledge on the safety and tolerability of JAK inhibitors in dermatology, focusing on adverse effects, to advise clinical practice and guide future research. A systematic literature search identified studies reporting on the adverse effects of JAK inhibitors in dermatological treatments. The review highlights common adverse effects, including infections, hematological changes, and increased risks of malignancies and cardiovascular events. Despite these concerns, JAK inhibitors are generally well-tolerated, with most adverse effects being manageable. Quality assessments of included studies indicate a moderate level of evidence, pointing to the need for ongoing surveillance and research. The findings underscore the importance of careful patient selection, monitoring, and management strategies to mitigate the risks associated with JAK inhibitor therapy. Further long-term studies are essential to fully understand the safety profile of these drugs and their impact on patient outcomes. The review supports the development of clinical guidelines for the use of JAK inhibitors, emphasizing risk assessment, patient education, and regular monitoring. It also highlights the need for post-marketing surveillance to capture real-world data on the long-term safety and efficacy of these treatments.

Keywords: *JAK Inhibitors, Dermatology, Safety, Tofacitinib, Ruxolitinib.*
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INTRODUCTION
The establishment of Janus kinase (JAK) inhibitors in dermatological practice has marked a significant improvement in the management of various skin conditions. JAK inhibitors work by selectively blocking the activity of one or more of the JAK family members (JAK1, JAK2, JAK3, and TYK2). These small molecules target the JAK-STAT signaling pathway, which plays a fundamental role in the pathogenesis of many inflammatory and auto-immune diseases, including psoriasis, atopic dermatitis, and alopecia areata [1]. The ability of JAK inhibitors to modulate immune responses offers a promising therapeutic avenue for conditions that have been challenging to manage with traditional therapies.

However, the introduction of any new therapeutic class necessitates a thorough understanding of its safety profile. Clinical and laboratory monitoring are essential components of this process, ensuring that the advantages of JAK inhibitors outweigh the risks associated with their use. Adverse events, ranging from minor to severe, have been documented, highlighting the importance of vigilance in the clinical application of these drugs [2].

Figure 1: Selectivity of several JAK inhibitors and JAK-STAT pathway inhibition. Psoriatic arthritis (PsoA), rheumatoid arthritis (RA), ulcerative colitis (UC), atopic dermatitis (AD), ankylosing spondylitis (AS), myelofibrosis (MF), PV polycythemia vera, and graft-versus-host disease (GvHD). The FDA has only approved topical ruxolitinib for vitiligo and AD.

The review aims to synthesize current knowledge on the safety of using JAK inhibitors in dermatology, emphasizing the need for clinical and laboratory monitoring. By examining the mechanisms of action, therapeutic potential, and reported adverse effects, provides a comprehensive overview to guide clinicians in the safe and effective use of JAK inhibitors in their practice.

The review article synthesizes current knowledge on the safety and tolerability of Janus kinase (JAK) inhibitors in dermatology, focusing on adverse effects to inform clinical practice and guide future research. Key questions include: What are the common adverse effects of JAK inhibitors in dermatological treatments? How manageable are these effects? What is the quality of evidence on JAK inhibitor safety? What are the implications for patient selection, monitoring, and management? How can ongoing surveillance contribute to understanding long-term safety? Additionally, what are the specific dermatologic adverse reactions and their impact on patient care? Overall, the review aims to provide insights into JAK inhibitor safety, clinical utility, and areas for further investigation.

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METHODOLOGY

In this narrative review, to assess the safety and tolerability of JAK inhibitors in dermatology, a systematic literature search was conducted across databases like PubMed, EMBASE, Cochrane Library, and Web of Science, focusing on studies reporting adverse effects in dermatological treatments from 2013 to 2023. The methodology included screening for relevant articles using keywords related to JAK inhibitors and dermatology such as "JAK inhibitors," "dermatology," "safety," "adverse effects," "tolerability," and specific drug names (e.g., "tofacitinib," "ruxolitinib," "baricitinib"), applying inclusion criteria that favored studies on human subjects with dermatological conditions treated with JAK inhibitors, and excluding non-English and non-relevant studies. Data on study design, adverse effects, and patient results were extracted and synthesized through a narrative approach due to the heterogeneity of the data. Quality assessment tools specific to each study design were employed to evaluate the evidence's strength, ensuring research integrity and transparency. This comprehensive approach aimed to collate existing data on JAK inhibitor safety in dermatology, providing a foundation for clinical decision-making and identifying areas for future research.

DISCUSSION

Mechanism of Action

The JAK-STAT pathway is essential for the transmission of extracellular signals to the cell nucleus, leading to gene expression changes. This pathway is activated when cytokines or growth factors bind to their particular cell surface receptors. The binding triggers the activation of JAKs, which are correlated with the intracellular domain of these receptors. Activated JAKs then phosphorylate STAT proteins, which dimerize and translocate to the nucleus to regulate gene expression. JAK inhibitors selectively block the activity of one or more of the JAK enzymes, thereby interrupting this signaling cascade and the subsequent gene expression that drives inflammation and cell proliferation.

Clinical Utility

JAK inhibitors have demonstrated noteworthy effectiveness in the management of many dermatological ailments. For example, tofacitinib, a JAK inhibitor, has shown promise in the therapy of moderate to severe plaque psoriasis in terms of lowering skin lesions and enhancing patient quality of life [3]. JAK inhibitors such as baricitinib and upadacitinib have also demonstrated encouraging outcomes in atopic dermatitis lessening the severity of the condition and itching [4]. Additionally, JAK inhibitors have become a viable therapy option for alopecia areata, an autoimmune disorder that results in hair loss, providing hope for hair growth in individuals who do not respond to conventional medications.

The clinical utility of JAK inhibitors extends beyond dermatology, with applications in rheumatology for conditions such as rheumatoid arthritis, where they have been shown to reduce joint damage and improve physical function [5]. Their use is also being explored in other inflammatory and autoimmune diseases, highlighting their versatility as a therapeutic option.

JAK Inhibitors: A Long-Term Use in Dermatology

Over time, the usage of inhibitors of JAK in dermatology has changed dramatically, resulting in a paradigm shift in the way that different dermatologic disorders are treated. This development is a result of the increasing knowledge of the function of the JAK-STAT pathway in skin disorders and the potential benefits of tailored treatments for bettering patient outcomes.

Early Exploration and Initial Approval

The journey of JAK inhibitors in dermatology began with the recognition of their potential beyond hematologic and rheumatologic disorders. Initial studies focused on their immunomodulatory effects, which suggested a possible role in treating inflammatory skin diseases. Tofacitinib initially approved for rheumatoid arthritis, was among the first to be explored for dermatologic use due to its broad immunosuppressive effects.

Expansion into Psoriasis and Atopic Dermatitis

Subsequent clinical trials exhibited the efficacy of tofacitinib in psoriasis, leading to a deeper investigation into the use of JAK inhibitors for skin conditions [6]. This period marked the expansion of JAK inhibitor applications to include atopic dermatitis, a generalized inflammatory skin condition that has few therapeutic alternatives. Studies showed that JAK inhibitors could significantly reduce the signs and symptoms of atopic dermatitis, offering a new therapeutic avenue for patients [7].

Breakthrough in Alopecia Areata

The finding that JAK inhibitors are successful in treating alopecia areata, an auto-immune condition characterized by non-scarring hair loss, marked an important milestone. JAK inhibitors have demonstrated the ability to treat autoimmunity at the hair follicle level by causing hair regrowth in alopecia areata patients, according to clinical trials [8].

Recent Advances and Future Directions

More recently, the development and approval of newer JAK inhibitors have broadened the therapeutic landscape in dermatology. Ruxolitinib, for instance, has been approved for the therapy of atopic dermatitis, underscoring the growing acceptance and integration of JAK inhibitors into dermatologic practice.

Figure 2: FDA approval timeline for JAK inhibitors used in dermatology [9]. The future of JAK inhibitors in dermatology looks promising, with ongoing research exploring their use in other skin conditions such as vitiligo

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and psoriatic arthritis. The potential for developing more selective JAK inhibitors also holds the promise of minimizing side effects while maximizing therapeutic benefits.

JAK Inhibitors' Tolerability and Safety

The development of JAK inhibitors has resulted in a new era in the treatment of inflammatory and autoimmune diseases, which includes a variety of dermatological disorders. The JAK-STAT signaling system, which is essential to the etiology of many illnesses, is the target of these drugs. While JAK inhibitors have shown considerable efficacy, their safety and tolerability are subjects of ongoing research and discussion within the medical community. This elaboration delves deeper into the safety concerns associated with JAK inhibitors and their overall tolerability, supported by citations from the literature.

JAK inhibitors are subject to a black box warning from the U.S. Food and Drug Administration (FDA) as a result of serious safety issues found in post-marketing surveillance and clinical trials. Data indicating a higher risk of major heart events, cancer, blood clots, and mortality linked to these drugs was the main factor behind this decision. The ORAL Surveillance trial was a key investigation that led to this move. It was a post-marketing requirement to assess the safety of tofacitinib vs tumor necrosis factor (TNF) inhibitors. In comparison to individuals receiving TNF blockers, the research found that those treated with tofacitinib, a JAK inhibitor, had a greater incidence of major adverse cardiovascular events (MACE) and malignancies, except non-melanoma skin cancer [10].

These outcomes prompted the FDA to re-estimate the risk-benefit report of JAK inhibitors, leading to the implementation of the black box warning to ensure healthcare providers and patients are aware of these potential risks. The warning aims to guide clinicians in making informed decisions about prescribing these drugs, emphasizing the need for careful patient selection and monitoring [11].

Safety Concerns

Infections

Concerns regarding a higher risk of infections are raised by JAK inhibitors' immunosuppressive effects. Individuals on these medications may show increased vulnerability to a wide range of pathogens, such as bacteria, viruses, and fungi. those treated with JAK inhibitors have seen significantly increased rates of serious infections, including TB and opportunistic infections like herpes zoster when compared to those receiving biologics or conventional disease-modifying antirheumatic medications (DMARDs) [12]. This means that during therapy, there must be strict screening for latent infections and constant observation for the emergence of new infections.

Hematological Effects

JAK inhibitors can impact hematopoiesis, leading to changes in blood cell counts. Anemia, neutropenia, and lymphopenia are among the hematological effects observed, attributed to the inhibition of JAK2, a kinase involved in the signaling pathways of several growth factors essential for blood cell production [1]. Regular monitoring of complete blood counts is recommended to detect and manage these effects promptly.

Cardiovascular Risks and Thrombosis

Research points to a link between using JAK inhibitors and a higher risk of venous thromboembolism and cardiovascular events, especially at higher doses. This correlation emphasizes how crucial it is to evaluate patients' cardiovascular risk factors before starting therapy and how crucial it is to continuously check for symptoms of thrombosis and cardiovascular disease while receiving treatment.

Malignancies

The potential for an increased risk of malignancies with long-term use of JAK inhibitors is a concern, given their immunosuppressive mechanism. While data on this risk are still emerging, the possibility of an elevated cancer risk warrants careful consideration, especially in patients with a history of malignancies or those at high risk for cancer [11].

Tolerability

Despite these safety concerns, JAK inhibitors are generally well-tolerated by most patients, with many experiencing significant improvements in their disease symptoms without severe adverse effects. Headaches, gastrointestinal symptoms like diarrhea, and upper respiratory tract infections are typical adverse effects. Usually mild to moderate in severity, these side effects are easily controlled with supportive care or dose modifications.

The tolerability of JAK inhibitors may vary based on the specific agent and patient characteristics, including age, comorbid conditions, and concomitant medications. Clinical trials and real-world studies have provided valuable insights into the side effect profiles of different JAK inhibitors, facilitating informed decision-making in clinical practice [10].

Monitoring and Management

Effective management of patients on JAK inhibitors involves a comprehensive approach that includes careful patient selection, thorough pre-treatment evaluation, and diligent monitoring for adverse effects. Strategies to optimize safety include screening for latent tuberculosis, regular monitoring of blood counts and lipid profiles, assessment of liver and kidney function, and vigilance for signs of infection or malignancy. Adjusting the dosage or discontinuing the medication may be necessary for

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patients who develop significant adverse effects or those who are at high risk for complications.

JAK inhibitors represent a significant advancement in the treatment of inflammatory and auto-immune diseases, offering new hope for patients with conditions that were previously difficult to manage. While their introduction has been a milestone in therapeutics, the safety and tolerability of these agents continue to be areas of active research. Ongoing studies and post-marketing observation are critical for further elucidating the long-term safety profile of JAK inhibitors and for developing strategies to mitigate their risks, ensuring that the benefits of these innovative treatments can be maximized for patients.

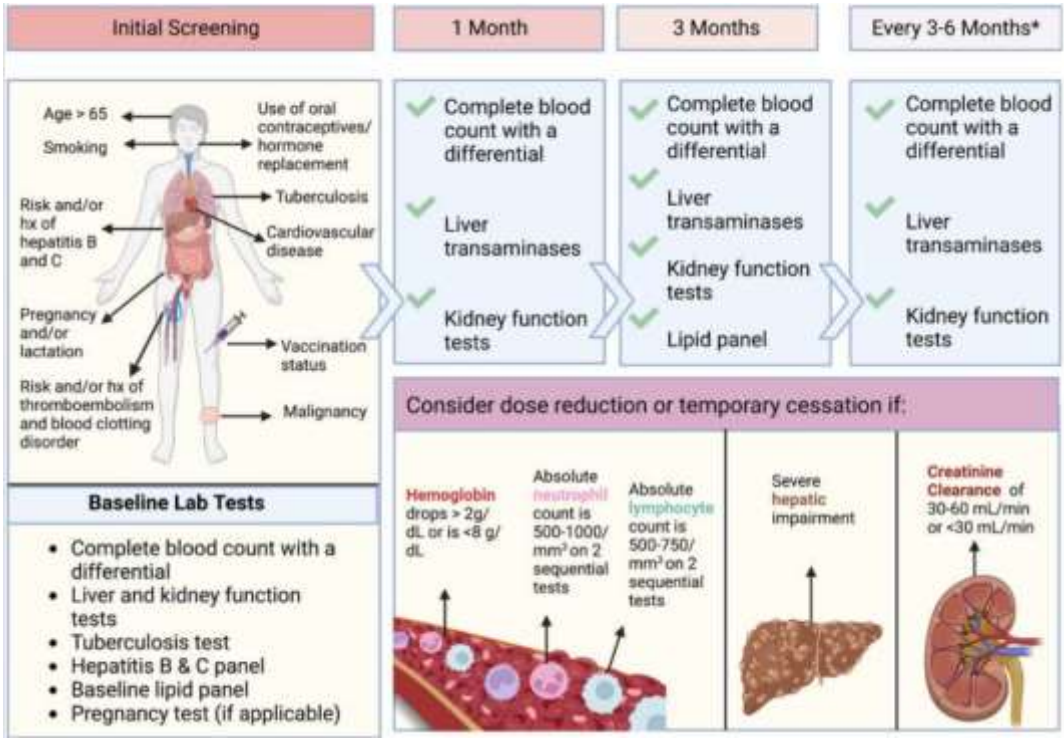

Figure 3: Screening and tracking of test results for individuals using JAK inhibitors. *Based on previous lab findings and risk factors for the patient

Adverse Reactions in Dermatology

JAK inhibitors, while providing significant therapeutic benefits for various inflammatory and autoimmune conditions, including dermatological diseases, have been related to a range of dermatologic side effects. The intensity and frequency of these side effects can vary, which can affect the individual's quality of life and adherence to therapy. Understanding these dermatologic adverse effects is crucial for clinicians to manage and mitigate potential risks associated with JAK inhibitor therapy.

Acne and Acneiform Eruptions

Acne and acneiform eruptions have been stated in individuals treated with JAK inhibitors. These skin conditions are thought to arise due to the modulation of immune pathways that affect skin homeostasis. Tofacitinib, for example, has been associated with the development of acne in clinical trials, particularly in younger patients and those with a history of acne.

Eczema and Atopic Dermatitis

Although JAK inhibitors are used to treat atopic dermatitis, paradoxical eczema or exacerbation of pre-existing atopic dermatitis has been observed in some cases. This phenomenon suggests a complex interaction between the JAK-STAT pathway and the pathophysiology of eczema, requiring further investigation.

Herpes Zoster

An increased risk of shingles infection has been noted among individuals taking JAK inhibitors. This risk is attributed to the immunomodulatory effects of these drugs, which may compromise the immune system's ability to control latent viral infections. The incidence of herpes zoster appears to be higher in individuals treated with JAK inhibitors compared to those on traditional DMARDs or biologics [13].

Non-Melanoma Skin Cancer

There is rising evidence to suggest a correlation between long-term use of JAK inhibitors and an increased risk of non-melanoma skin cancer, including basal cell

carcinoma and squamous cell carcinoma. This risk underscores the importance of regular skin examinations and sun protection measures for patients undergoing JAK inhibitor therapy [12].

Alopecia

While JAK inhibitors have shown promise in treating alopecia areata, cases of hair loss or worsening of alopecia have been reported in patients using these medications for other indications. The exact mechanism behind this adverse effect remains unclear and warrants further study [14].

The dermatologic side effects of JAK inhibitors highlight the need for comprehensive dermatologic assessment and monitoring in patients receiving these treatments. Clinicians should be vigilant for the emergence of skin-related adverse effects and consider these in the context of the overall risk-benefit analysis of JAK inhibitor therapy. Patient education on the potential for dermatologic side effects and strategies for skin care and protection are also essential components of management.

FUTURE RESEARCH

In clinical practice, the review underscores the importance of vigilance in monitoring patients receiving JAK inhibitors for dermatological conditions due to the identified adverse effects, including infections, hematological changes, cardiovascular events, and increased malignancy risks. While generally well-tolerated, there are limitations in capturing all potential adverse events, suggesting the need for comprehensive patient assessment and ongoing surveillance. Policymakers should consider these findings when developing guidelines for JAK inhibitor use in dermatology, ensuring that they address challenges in implementation and adaptation to diverse healthcare settings. Future research should focus on filling knowledge gaps, particularly regarding long-term safety profiles, optimizing monitoring strategies, and refining clinical guidelines to enhance patient outcomes and safety in JAK inhibitor therapy for dermatological conditions.

CONCLUSION

JAK inhibitors have shown strong effectiveness in certain skin conditions that significantly affect quality of life. Using information from clinical trials, healthcare professionals can offer more informed guidance to patients regarding treatment choices. Healthcare providers should have collaborative discussions with their patients regarding the advantages and disadvantages of an individualized approach.

Limitations

Key findings from this review on JAK inhibitors' safety in dermatology highlight common adverse effects like infections, hematological changes, cardiovascular events, and malignancy risks, albeit with limitations in capturing all potential adverse events' severity and incidence. While generally well-tolerated, subjective tolerability assessments and reporting biases may influence conclusions, and gaps in capturing rare or long-term adverse effects remain. Moderate evidence quality from included studies suggests limitations in study design and methodological rigor, impacting reliability. Ongoing surveillance and research are advocated, but specific recommendations for enhancing monitoring practices are lacking. Support for clinical guideline development for JAK inhibitor use is provided, but challenges in guideline implementation and adaptation are not fully addressed.

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List of abbreviations

JAK - Janus Kinase
STAT - Signal Transducer and Activator of Transcription
RCT - Randomized Controlled Trial
DMARDs - Disease-Modifying Antirheumatic Drugs
MACE - Major Adverse Cardiovascular Events
FDA - Food and Drug Administration
TNF - Tumor Necrosis Factor
EMBASE - Excerpta Medica Database
AD - Atopic Dermatitis
PsoA - Psoriatic Arthritis
RA - Rheumatoid Arthritis
UC - Ulcerative Colitis
AS - Ankylosing Spondylitis
MF - Myelofibrosis
PV - Polycythemia Vera
GvHD - Graft-versus-Host Disease

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Conflict of interest

The authors have no competing interests to declare.

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