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SYSTEMATIC REVIEW

Advances in the use of Ruxolitinib in the treatment of vitiligo disease

Avances en el uso de Ruxolitinib en el tratamiento de la enfermedad de vitiligo

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ABSTRACT

Introduction: Vitiligo is an acquired autoimmune hypomelanosis, associated with a genetic component, whose expression is usually triggered by environmental factors. Its typical symptoms are hypopigmented or apigmented macules with a progressive behavior, which makes it a relatively easy pathology to diagnose. First-generation JAK inhibitors, such as ruxolitinib, baricitinib, delgotinib and tofacitinib, are less selective and inhibit different JAKs. Therefore, JAKi could expand treatment options for various inflammatory skin diseases. By reducing the effect of all cytokines that are activated by the corresponding JAK/STAT pathway, they may be more effective than classical biologics that target a single cytokine. **Objectives:** to describe the scientific evidence on the efficacy and safety of advances in the use of Ruxolitinib in the treatment of vitiligo disease compared to other conventional treatments or placebo, in terms of skin repigmentation, symptom improvement and occurrence of adverse events.
Material and methods: a search was performed in Pubmed, Scopus, Web of Science from January 2000 to October 2022. Selecting abstracts of cohort and case-control studies evaluating the use of Ruxolitinib in the treatment of vitiligo disease in comparison with other conventional treatments or placebo, in terms of skin repigmentation, symptom improvement and occurrence of adverse events.
Results: the results of this systematic review support the efficacy of ruxolitinib cream in the treatment of vitiligo, with significant improvements in repigmentation observed in different patient subgroups. Despite some limitations, these findings are encouraging and suggest that ruxolitinib cream may be an effective and safe treatment option for vitiligo, especially in the context of facial repigmentation. However, more research is needed to confirm these results and to better understand the mechanisms involved in this treatment. This encourages further research in this area and provides hope for patients struggling with vitiligo.

Keywords: Vitiligo; Janus Kinase Inhibitors; Ruxolitinib; Systematic Review.

RESUMEN

Introducción: el vitíligo es una hipomelanosis autoinmune adquirida, asociada a un componente genético, cuya expresión suele estar desencadenada por factores ambientales. Sus síntomas típicos son máculas hipopigmentadas o apigmentadas con un comportamiento progresivo, lo que la convierte en una patología relativamente fácil de diagnosticar. Los Inhibidores de JAK de primera generación, como ruxolitinib, baricitinib, delgotinib y tofacitinib, son menos selectivos e inhiben diferentes JAK. Por lo tanto, los JAKi podrían ampliar las opciones de tratamiento para varias enfermedades inflamatorias de la piel. Al reducir el efecto de todas las citoquinas que son activadas por la vía JAK/STAT correspondiente, pueden ser más efectivos que los productos biológicos clásicos que se dirigen a una sola citoquina.
Objetivos: describir la evidencia científica sobre la eficacia y seguridad de los avances en el uso de Ruxolitinib en el tratamiento de la enfermedad de vitiligo en comparación con otros tratamientos convencionales o placebo, en términos de repigmentación de la piel, mejoría de los síntomas y ocurrencia de eventos adversos.
Material y métodos: se realizó una búsqueda en Pubmed, Scopus, Web of Science desde enero de 2000 hasta octubre de 2022. Seleccionando resúmenes de estudios de cohorte y de casos y controles que evalúen uso de Ruxolitinib en el tratamiento de la enfermedad de vitiligo en comparación con otros tratamientos convencionales o placebo, en términos de repigmentación de la piel, mejoría de los síntomas y ocurrencia de eventos adversos.
Resultados: los resultados de esta revisión sistemática respaldan la eficacia de ruxolitinib cream en el tratamiento del vitiligo, con mejoras significativas en la repigmentación observadas en diferentes subgrupos de pacientes. A pesar de algunas limitaciones, estos hallazgos son alentadores y sugieren que ruxolitinib cream puede ser una opción de tratamiento efectiva y segura para el vitiligo, especialmente en el contexto de la repigmentación facial. Sin embargo, se necesita más investigación para confirmar estos resultados y comprender mejor los mecanismos involucrados en este tratamiento. Esto motiva la realización de futuras investigaciones en esta área y brinda esperanza a los pacientes que luchan contra el vitíligo.

Palabras clave: Vitiligo; Janus Kinase Inhibitors; Ruxolitinib; Systematic Review.

INTRODUCTION

Vitiligo is an acquired autoimmune hypomelanosis, associated with a genetic component, whose expression is usually triggered by environmental factors. Its typical symptoms are hypopigmented or apigmented macules with a progressive behavior, which makes it a relatively easy pathology to diagnose. Vitiligo usually affects visible areas of the body and can usually have a great emotional impact on the patient, affecting self-esteem, so psychotherapy is an essential part of the treatment. The goal of treatment is to halt the progression of the disease, promote hyperpigmentation and prevent relapse.[1]

It is the most common depigmenting disorder worldwide. It is due to the loss of functional melanocytes due to autoimmune attack. This attack is closely related to the individual's genetics, as well as to the environmental risk factors to which he or she is exposed. It is important to recognize the different patterns of vitiligo, as they can predict disease progression and response to treatment.[1]

It affects 0,5-1 % of the world's population, regardless of race or gender, and it has been observed that more than 50 % of cases occur before the age of 20.[2]

This pathology usually presents as acromic and hypochromic macules, with defined borders and a tendency to symmetry. The topography of the lesions is ubiquitous, with a preference for the acral

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and periorificial areas on the face, and in sites exposed to trauma (Koebner phenomenon) and, less frequently, in the dorsal area.[3,4]

From the point of view of its pathogenesis it is known to be a polygenic and multifactorial disease, and it has been described that the pathology results from a dynamic interaction of genetic and environmental factors which lead to an autoimmune attack on melanocytes.[5]

Important aspects related to the development of the disease are described below.

Genetic factor

The importance of genetics in the risk of developing vitiligo has been demonstrated by identifying specific genes encoding innate immunity (e.g., NLRP1, IFIH1, CASP7, C1QTNF6, TRIF, TICAM1 and others encoding adaptive immunity (e.g., FOXP3, BACH2, CCR CD80, PTPN22, IL2R, αGZMB HLA class I and II, CTLA4) thus demonstrating the link to the immune system. Each of the alleles evaluated has a different specific function which are being investigated as a possible therapeutic target. For example, mutations in the DDR1 gene cause characteristic defects in melanocytes.[5]

Oxidative stress

Melanocytes in patients with vitiligo have intrinsic defects that decrease their ability to reduce environmental stress. Therefore, the interaction between vulnerable melanocytes and environmental components increases the generation of reactive oxygen species (ROS), causing oxidative stress leading to cell destruction.[6]

Environmental factor

Exposure to certain chemical compounds on the skin, followed by a lack of pigmentation shows the relationship between environmental factors and vitiligo. Phenols, for example, which are often found in hair dyes, adhesives, industrial oils, paints and leather, can act as a tyrosine analog in melanocytes, increasing oxidative stress, and thus the most vulnerable areas are the upper extremities and beard in adults; however, in children it occurs mainly in the lower extremities.[7]

Immunity factor

As mentioned above, oxidative stress in genetically predisposed individuals leads to local inflammatory responses and activation of innate immune processes, resulting in a specific cytotoxic immune response against melanocytes. In addition, an autoimmune role in vitiligo has been demonstrated through the presence of anti-melanocyte antibodies, associations with polymorphisms, perilesional T-cell infiltration and cytokine expression, and associations with other autoimmune diseases.[8]

Clinically, it manifests with asymptomatic macules and depigmented plaques without signs of inflammation. They can be located on any area of the skin and mucosa, but are more frequent on the face, hands, periorificial area and genitalia. They can also affect the pigment epithelium of the retina and uvea. Its clinical course is unpredictable: it may be stable or develop slowly or rapidly over time. There are two clinical classifications:[5]

- Non-segmental vitiligo (NSV). The most common, which is usually bilateral and symmetrical. It has variants such as generalized vulgar, acrofacial, mucosal, local, focal and generalized; and
- Segmental vitiligo (SV). With a pattern of depigmentation usually of a unilateral dermatome. (Romain and Farber, no date) VITILIGO 04

Non-segmental vitiligo, also known as vitiligo vulgaris, is the most common manifestation of the disease. It presents as an achromic or hypochromic macule, usually bilateral, often symmetrical, preferentially on the acral area, periorificial and extensor limbs. In addition, one third of patients

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with vitiligo suffer from clinical Köbner's phenomenon, mainly on the palms and arms. The behavior of SNV tends to be gradual and unpredictable over time.[9]

Segmental vitiligo accounts for only 5 to 15 % of vitiligo cases. The most commonly affected population is children. It usually presents as unilateral depigmented plaques of linear or massive distribution, mainly on the face. Its manifestations are sudden, even within days or weeks, with a rapidly progressive behavior; it stabilizes in 1-2 years, usually without risk of affecting other parts of the body. VS is less responsive to treatment than VNS because it is associated with leukotrichia, thus has less melanocyte reserve available for repigmentation.[10]

In general, the diagnosis of vitiligo is clinical. In the clinical history it is extremely important to ask about age of onset, site of first lesion, time to stabilization, rate of progression, sites involved (including genitalia), triggers such as friction and trauma, occupation, and whether there are depressive symptoms and their impact on quality of life. There are many entities that may resemble vitiligo mainly in the early stages of the disease. The physical examination will reveal the presence of the aforementioned macules, of which the prevalence, morphology, mucosal involvement, percentage of body surface involvement, presence of leukotrichia, Köbner's phenomenon, confetti-like depigmentation, signs of autoimmune disease, halo nevi and repigmentation patterns should be determined. Occasionally, it may be necessary to use a Wood's lamp to distinguish depigmented vitiligo lesions from other hypopigmented conditions; in addition, it is useful in patients with pale skin and difficult-to-distinguish lesion borders. Histologic confirmation may be necessary in suspicious cases with biopsy, which shows melanocytes with a small amount of melanin granules at the edge of the macules. Occasionally lymphoid infiltration may be seen at the active border of the lesion. It should be noted that, due to the association with other diseases, additional tests are recommended, such as: blood count, fasting glucose level, vitamin D and B12 levels, TSH, T3, free T4.[11]

It is recommended to start treatment as soon as possible after diagnosis to achieve adequate physical and emotional results. The treatments available to date do not cure the disease, they only stop or maintain it, there are several different treatments to treat this condition.[12]

The main goals of treatment are to stop the progression of the disease, repigmentation of lesions and prevention of relapses. To choose the appropriate treatment, it is necessary to determine the stability of the disease, its extent and duration. Stable vitiligo is defined as the absence of disease progression for at least six months to two years, while unstable vitiligo refers to the appearance of new lesions or their enlargement. It is of great importance that, because vitiligo significantly affects the quality of life, all patients should receive psychotherapy.[13]

The different treatments can be divided into those aimed at halting the progression of the disease and those aimed at repigmentation of the lesions. Both can be performed at the same time:

Topical corticosteroids: the anti-inflammatory effect of moderate and high potency topical corticosteroids, manage to stop the progression of the disease and help repigmentation, so they are considered the first line treatment for the disease. But in turn, the use of combination therapy is recommended. NB-UVB is one of the mainstays of treatment, and its efficacy can be improved in combination with other therapies. NB-UVB is rarely used as monotherapy. Often a combination of systemic steroids and phototherapy is used to halt the progression of depigmentation.[14]

Monoclonal antibodies are specialized glycoproteins produced by combining stem cells and B-lymphocyte clones (hybridomas). Monoclonal antibodies (mAbs) are increasingly important in the treatment of various diseases as well as in clinical diagnostics due to their high specificity and homogeneity. Today, mAbs are used in a wide range of pathologies, from the treatment of cancer and autoimmune diseases like Vitiligo, to applications in ophthalmology, asthma, etc.[15]

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) intracellular signaling pathway is activated by the binding of extracellular ligands to various transmembrane receptors. Janus kinases (JAKs) are a family of tyrosine kinases that act as signal transducers in cells and include the

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JAK1, JAK2, JAK3 and TYK2 molecules. JAKs function by forming dimers in the cytoplasmic part of cytokine receptors. These JAK dimers can bind to multiple receptors and are activated by various cytokines, thereby activating various STAT proteins (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT61) and thus participating in specific biological functions. After activation, STAT proteins associate to form dimers and can move to the nucleus. There they act as transcription factors to regulate genes responsible for the production of proinflammatory cytokines and growth factors. The JAK/STAT pathway is therefore a therapeutic target for various immune-mediated inflammatory diseases. JAK inhibitors (JAKi) are small molecules that inhibit JAK kinase activity and potently reduce intracellular transduction of the JAK/STAT pathway.[16]

The JAK/STAT pathway is a therapeutic target for several immune-mediated inflammatory diseases. JAK inhibitors (JAKi) are small molecules that inhibit JAK kinase activity and potently reduce intracellular transduction of the JAK/STAT pathway.[17]

First-generation JAKi, such as ruxolitinib, baricitinib, delgotinib, and tofacitinib, are less selective and inhibit different JAKs. Therefore, JAKi could expand treatment options for various inflammatory skin diseases. By reducing the effect of all cytokines that are activated by the corresponding JAK/STAT pathway, they may be more effective than classical biologics that target a single cytokine.[18]

JAKi have an acceptable risk-benefit profile. Most side effects described were mild to moderate; the most common were upper respiratory tract, urinary tract, and gastrointestinal tract infections.[19]

Dysregulation of the JAK/STAT signaling pathway has been demonstrated in several dermatologic inflammatory diseases, with differences in JAK expression in healthy and diseased skin biopsies. JAK molecules are overexpressed in the epidermis and/or dermis such as in psoriasis, cutaneous lupus erythematosus, pyoderma gangrenosum, atopic dermatitis (AD) and alopecia areata (AA). JAK3 expression is significantly increased in the epidermis of these diseases.[20]

Elevated levels of interferon-γ (IFN γ) and related cytokines CXCL9 and CXCL10 have been observed in human skin with vitiligo. Through JAK1/243, IFNγ activates the transcription of CXCL9 and CXCL10, which is necessary for the recruitment of cytotoxic T lymphocytes, the main effector cells responsible for melanocyte destruction. Therefore, inhibition of JAKs may be an effective therapeutic strategy in the treatment of vitiligo, thereby reducing the production of CXCL9 and CXCL10.[21]

It would then be understood that Janus kinase inhibitors (JKIs) such as tofacitinib and ruxolitinib stop the vitiligo process and achieve repigmentation. They could even be combined with BE-UVB as part of the treatment of the disease. However, relapse has been observed after discontinuation of JAKi treatment, possibly caused by the presence of autoreactive memory cells resident in the skin. IL-15, whose expression is increased in the epidermis of vitiligo, is thought to play an important role in CD8 maintenance, suggesting that it could be an effective targeted therapy in patients with vitiligo.[17]

Objective: to describe the scientific evidence on the efficacy and safety of advances in the use of Ruxolitinib in the treatment of vitiligo disease compared to other conventional treatments or placebo, in terms of skin repigmentation, symptom improvement and occurrence of adverse events.

METHODS

Study Design

Taking into account that there is abundant scientific literature on the subject under study, the research results will be synthesized by means of a systematic review. If the quantitative data are sufficiently standardized, a meta-analysis will be performed.

This systematic review will follow the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[22]

Study population

Scientific Papers addressing use of Ruxolitinib in the treatment of vitiligo disease in comparison to other conventional treatments or placebo, in terms of skin repigmentation, symptom improvement and occurrence of adverse events, in the period January 2000 to October 2022 will be included.

Inclusion Criteria

- Original articles with IMRyD typology that develop cohort studies, clinical trials, other systematic reviews and meta-analysis.

Exclusion Criteria

- Review articles, Scientific Letters/Letters to the Editor, Clinical Cases, Editorials, Original Articles that correspond to preclinical studies and Observational Studies.

Selection and Sample Size

A search will be conducted in Pubmed, Scopus, Web of Science from January 2000 to October 2022. Selecting abstracts of cohort and case-control studies evaluating use of Ruxolitinib in the treatment of vitiligo disease compared to other conventional treatments or placebo, in terms of skin repigmentation, symptom improvement and occurrence of adverse events.

Data collection planning

- A literature search will be performed in databases using as MESH descriptors: "Vitiligo" and "Ruxolitinib".
- The publications will be classified and, according to the inclusion and exclusion criteria, those that will make up the study will be selected.
- A critical reading of the abstracts and articles in extenso will be carried out to evaluate their inclusion according to their relevance.
- The studies will be classified according to the levels of evidence and quality.

Ethical and legal considerations

This study included secondary data sources and therefore does not correspond to an analysis from the ethical point of view, given that no experimentation or evaluations were performed on human beings/experimental animals.

RESULTS AND DISCUSSION

The main results of the studies included in this review indicate that the use of ruxolitinib in cream form has been shown to be effective in the treatment of vitiligo. Patients who received ruxolitinib cream showed significant improvements in the repigmentation of vitiligo lesions compared to the control group who received a vehicle without the drug. These improvements were observed in both facial and nonfacial lesions.[23,24,25]

In addition, a dose-dependent response was found, meaning that as the concentration of ruxolitinib in the cream and frequency of application increased, higher rates of repigmentation were observed.[26] This suggests that dose and frequency of application are important factors to consider when using ruxolitinib in the treatment of vitiligo.[16]

The results also showed that the group receiving ruxolitinib cream 1,5 % twice daily had the highest response rates in terms of achieving a 50 % or greater improvement from baseline in the Facial Vitiligo Area Score Index (F-VASI) at week 24. In addition, this group also showed the highest response rates in achieving scores of "clear or almost clear" on the Physician's Global Vitiligo Assessment of Vitiligo (F-PhGVA). These findings are important, as they suggest that higher concentration of ruxolitinib and higher frequency of application may lead to more positive outcomes in the treatment of vitiligo.[27]

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Study	Country	Aim	Intervention	Type of research	Sample	Main results	Clinical/practical implications
Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial	United States	Investigated the therapeutic potential of ruxolitinib cream in patients with vitiligo and report the efficacy and safety results up to 52 weeks of double-blind treatment.	Control: vehicle twice daily. Experimental Group: 0,15 % once daily group 0,5 % once daily group 1,5 % once daily group 1,5 % twice daily group	randomised, double-blind, dose-ranging, phase 2 study	GC: 32 patients GE: Total 157 participans (0,15 % once daily Group, n=31; 0,5 % once daily group, n=31; 1,5 % once daily group, n=30; 1,5 % twice daily group, n=33)	The study included 157 patients with vitiligo who were randomly assigned to receive ruxolitinib cream or vehicle. Patients receiving ruxolitinib cream showed significant improvements in repigmentation compared to the vehicle group. - The highest response in achieving a 50 % or higher improvement from baseline in facial Vitiligo Area Scoring Index (F-VASI50) was observed in the group receiving ruxolitinib cream 1,5 % twice daily. - Dose-dependent responses were observed, with higher doses of ruxolitinib cream leading to greater improvements in F-VASI and total body	Ruxolitinib cream shows promise as a potential treatment option for vitiligo, a chronic autoimmune disease causing skin depigmentation and reduced quality of life. - The study demonstrates that ruxolitinib cream leads to significant improvements in repigmentation of both facial and non-facial vitiligo lesions. - Dose-dependent responses were observed, with higher doses of ruxolitinib cream resulting in greater improvements in repigmentation. - The findings suggest that longer duration therapy with ruxolitinib cream allows for a more closely altered immune response and

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		Vitiligo Area Scoring Index (T-VASI). - Patients receiving ruxolitinib cream also had higher rates of reaching scores of clear or almost clear in the F-Physician Global Vitiligo Assessment (F-PhGVA) compared to the vehicle group. - Overall, ruxolitinib cream showed efficacy in improving repigmentation in both facial and non-facial vitiligo lesions, with continued improvement observed up to 52 weeks of treatment.	improved clinical outcomes. - The low frequency of application site reactions with ruxolitinib cream indicates its favorable tolerability compared to other topical therapies. - The reduction of serum CXCL10, an inflammatory chemokine associated with vitiligo pathogenesis, suggests that ruxolitinib cream may work by altering key pathways involved in the disease.
		Results of Ruxolitinib Administration in Different Subgroups: - The 0,15 % once daily group showed a response rate of 10 % in achieving a 50 % or higher improvement from	Overall, the results of this study suggest that ruxolitinib cream has the potential to be an effective and well-tolerated treatment option for patients with vitiligo, offering hope for improved repigmentation and quality of life.

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		baseline in facial Vitiligo Area Scoring Index (F-VASI50) at week 24 . - The 0,5 % once daily group had a response rate of 26 % in reaching F-VASI50 at week 24 . - The 1,5 % once daily group demonstrated a response rate of 30 % in achieving F-VASI50 at week 24 . - The 1,5 % twice daily group had the highest response rate of 36 % in reaching F-VASI50 at week 24 . - Dose-dependent responses were observed in both F-VASI and total body Vitiligo Area Scoring Index (T-VASI), with higher doses of ruxolitinib cream leading to greater improvements in repigmentation . - The 1,5 % twice daily group also showed the highest response rate in reaching F-VASI75 at	

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						week 52, with 52 % of patients achieving this level of improvement . - The 1,5 % twice daily group had the highest response rate in reaching T-VASI50 at week 52, with 36 % of patients achieving this level of improvement .	
Two Phase 3, Randomized, Controlled Trials of Ruxolitinib Cream for Vitiligo	France	The paper aimed to determine the effect and safety of ruxolitinib cream in patients with vitiligo and to compare its efficacy against a vehicle control.	TRuE-V1 Vehicle (N = 109) 1,5 % Ruxolitinib Cream (N = 221) Total (N = 330) TRuE-V2 Vehicle (N = 115) 1,5 % Ruxolitinib Cream (N = 228) Total (N = 343)	phase 3, double-blind, vehicle-controlled trials	674 patients were enrolled, 330 in TRuE-V1 and 344 in TRuE-V2.	In TRuE-V1, 29,8 % of patients in the ruxolitinib-cream group achieved at least a 75 % decrease in F-VASI at week 24, compared to 7,4 % in the vehicle group. In TRuE-V2, the percentages were 30,9 % and 11,4 %, respectively. Ruxolitinib cream demonstrated superiority over the vehicle control in achieving repigmentation of vitiligo lesions. Patients who applied ruxolitinib cream throughout 52 weeks experienced adverse events, with the most common being	The findings suggest that ruxolitinib cream could be a potential treatment option for patients with nonsegmental vitiligo, offering a non-invasive and topical approach. The improvements in vitiligo lesions reported by patients indicate that ruxolitinib cream may have a positive impact on their quality of life. However, it is important to note

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						application-site acne and pruritus. The results suggest that ruxolitinib cream could be a potential treatment option for patients with nonsegmental vitiligo, particularly for facial repigmentation.	that adverse events, such as application-site acne and pruritus, were reported with ruxolitinib cream.
Efficacy of ruxolitinib cream in vitiligo by patient characteristics and affected body areas: Descriptive subgroup analyses from a phase 2, randomized, double-blind trial	United states	The objective of the study was to evaluate the efficacy of ruxolitinib cream in treating vitiligo, a chronic autoimmune disease characterized by patches of depigmented skin. The study aimed to assess the treatment response of ruxolitinib cream in terms of repigmentation of facial and total body vitiligo lesions, as well as its impact on different body areas, including acral areas.	Ruxolitinib 1,5 % cream twice a day for 24 weeks	randomized, double-blind trial	157 adults patients	In the Phase 2 trial, ruxolitinib cream was observed to show trends of clinical activity in the treatment of vitiligo, with substantial repigmentation of vitiligo facial and body lesions after 24 weeks of treatment. Continued improvement was observed until week 52. F-VASI50 responses were observed in 40 % of patients previously treated with topical corticosteroids or topical calcineurin inhibitors and in two-thirds of	the study provides evidence for the efficacy of ruxolitinib cream in treating vitiligo, a chronic autoimmune disease characterized by depigmented skin patches. This has practical implications for clinicians and dermatologists in considering ruxolitinib cream as a treatment option for vitiligo patients . The findings suggest that ruxolitinib cream can produce substantial repigmentation of facial and total body vitiligo lesions, including difficult-to-repigment acral areas .

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		The study also aimed to analyze treatment response based on patient characteristics and affected body areas, including patients with longstanding and extensive disease, and those who had previously received topical corticosteroids or topical calcineurin inhibitors, or prior phototherapy.				patients receiving prior phototherapy. Ruxolitinib cream also produced clinically significant repigmentation of all body areas, including acral areas, which are notoriously difficult to repigment.	
Janus Kinase Inhibitors in the Treatment of Vitiligo: A Review	United states	The paper discusses the role of the JAK/STAT signaling pathway in the pathogenesis of vitiligo and how JAK inhibitors, such as ruxolitinib, baricitinib, and tofacitinib, can effectively target this pathway to treat the condition. The paper also highlights the need for further studies to determine the ideal dosage of JAK inhibitors for vitiligo treatment	ruxolitinib cream 1,5 % twice daily, 1,5 % once daily, and 0,5 % once daily achieved F-VASI50 than patients in the control groups. Patients who were assigned in the three positive responsive groups receiving ruxolitinib	clinical trials	157 patients	JAK inhibitors, including ruxolitinib, baricitinib, and tofacitinib, have shown effectiveness in treating vitiligo, supporting the implication of the IFN-g-chemokine signaling axis in the pathogenesis of the condition. Ifidancitinib, a dual JAK1 and JAK3 inhibitor, has been investigated for its efficacy in treating non-segmental	JAK inhibitors, such as ruxolitinib, baricitinib, and tofacitinib, have shown effectiveness in treating vitiligo, indicating the involvement of the IFN-g-chemokine signaling axis in the pathogenesis of the condition. Ifidancitinib, a dual JAK1 and JAK3 inhibitor, has been investigated for its efficacy in treating non-segmental facial vitiligo.

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		and to explore other inflammatory pathways involved in the development of the disease	cream 1,5 %twice daily, 1,5 % once daily, and 0,5 % once daily were asked to remain their original treatment dose up to 52 weeks		facial vitiligo, and a phase 2 study showed improvement in F-VASI and the Vitiligo Noticeability Scale (VNS) in patients treated with ifidancitinib solution. Baricitinib, a selective JAK1 and JAK2 inhibitor, has shown potential for repigmentation in vitiligo lesions, as observed in a case report where a patient noticed complete repigmentation when switching from tofacitinib to baricitinib.	Baricitinib, a selective JAK1 and JAK2 inhibitor, has shown potential for repigmentation in vitiligo lesions. A new study is currently being conducted to evaluate the safety and efficacy of combining baricitinib with phototherapy for vitiligo treatment.
Repigmentation in vitiligo using Janus kinase (JAK) inhibitors with phototherapy: systematic review and meta-analysis	Australia	To determine the expected response of vitiligo to JAK inhibitor therapy and factors which influence response rates.		systematic review and meta-analysis	From the 9 eligible studies, individual patient data from 45 cases were pooled. Good response was achieved in 57,8 %, partial response in 22,2 %, and none or minimal response in 20 % of cases. When subgrouped according to site, facial vitiligo had	JAK inhibitors, such as tofacitinib and ruxolitinib, show promising results in the treatment of vitiligo, an autoimmune disorder characterized by depigmentation of the skin. Concurrent UVB phototherapy appears to enhance the efficacy of JAK

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				the highest good response rate (70 %), compared toextremities (27,3 %) and torso/non-sun exposed areas (13,6 %).	inhibitors in vitiligo treatment. The response rates to JAK inhibitor therapy vary depending on the site of vitiligo. Facial vitiligo has the highest good response rate compared to extremities and torso/non-sun exposed areas. The findings of this systematic review and meta-analysis suggest that JAK inhibitors, especially when combined with phototherapy, could be a potential treatment option for vitiligo.
Vitiligo Skin T Cells Are Prone to Produce Type 1 and Type 2 Cytokines to Induce Melanocyte Dysfunction and Epidermal Inflammatory Response Through Jak Signaling	USA	The objective of this paper was to investigate the complex cytokine network involved in vitiligo and its impact on epidermal cells, specifically melanocytes. The study aimed to understand the contribution of melanocytes to the pathogenesis of	NanoString technology and multiplex ELISA were used to analyze the secretome of vitiligo skin T cells and identify the cytokines involved in the immune response. RT-qPCR was performed to measure gene	Active vitiligo perilesional skin is characterized by prominent type 1 and type 2 associated immune responses, indicating the complexity of the disease. The vitiligo skin T-cell secretome downregulates melanocyte function and adhesion while	The study highlights the complex nature of vitiligo, with both type 1 and type 2 cytokines playing a role in inducing inflammatory responses in the epidermal cells. Jak inhibitors, such as ruxolitinib, could potentially be used to prevent the impact of T-cell mediated cytokines on the

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		vitiligo and their interaction with T cells in the disease process.		expression in epidermal cells in response to vitiligo skin T cells. LEGENDplex Human Th cytokines and Human CD8NK panels were used to analyze the cytokine profile of vitiligo skin T-cell supernatants.		increasing melanocyte mitochondrial metabolism and expression of inflammatory cytokines and chemokines by epidermal cells. The Jak1/2 inhibitor ruxolitinib strongly inhibits the effects of T cells on epidermal cells, highlighting its potential clinical benefit in vitiligo. Melanocytes in vitiligo not only serve as targets of T cells but also actively contribute to perpetuating inflammation. The cytokine network involved in vitiligo includes pathways related to cytokine- and chemokine-mediated signaling associated with both type 1 and type 2 cytokines.	epidermis and pigmentation, suggesting a potential clinical benefit in treating vitiligo. Melanocytes, which are the target of T cells in vitiligo, may actively contribute to perpetuating inflammation in the disease. This suggests that targeting the cytokine pathways involved in vitiligo, including those affecting melanocytes, could have therapeutic implications.
FDA approves Ruxolitinib (Opzelura) for	PAKISTAN	The objective of the paper is to discuss the FDA		The paper does not explicitly mention the methods used	This paper did not involve patients	The topical lotion has shown efficacy in producing even	FDA approval of Ruxolitinib (Opzelura) as an at-home

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Vitiligo Therapy: A breakthrough in the field of dermatology		approval of Ruxolitinib (Opzelura) as a breakthrough therapy for vitiligo, a condition that causes spots and patches of paler skin. The paper highlights the efficacy and safety profile of Ruxolitinib in treating vitiligo, as well as its potential to improve patients' self-esteem and quality of life The paper also emphasizes the need for further research to examine the drug's effectiveness and safety, as well as to acquire the latest information about its daily dose and administration		in the study. It primarily focuses on discussing the FDA approval of Ruxolitinib (Opzelura)		skin tones and potentially boosting patients' self-esteem. However, adverse effects such as acne, redness, itching, inflammation, headaches, and fever have been observed, necessitating the need for further studies to demonstrate its efficacy and safety. [	treatment for non-segmental vitiligo has significant practical implications in the field of dermatology. The topical lotion can be used twice daily to promote the development of new, healthy skin cells and reintroduce pigment to the affected area, resulting in even skin tones and potentially boosting patients' self-esteem. Compared to oral forms of the medicine, the topical lotion has a better safety profile, although adverse effects such as acne, redness, and itching at the application site, as well as other systemic effects, have been observed.
The use of Janus kinase inhibitors and narrowband ultraviolet B combination therapy in non-segmental vitíligo	Texas, USA	The objective of the paper is to discuss the use of Janus kinase (JAK) inhibitors in combination with narrowband ultraviolet B (NB-	Ruxolitinib 1,5 % cream BID 20 weeks Ruxolitinib 1,5 % cream BID 32-week extension	randomised, controlled, phase 2 trial	674 patients with non-segmental vitiligo	The paper does not explicitly mention the results of any specific study or clinical trial. However, it discusses the use of Janus kinase (JAK)	the use of Janus kinase (JAK) inhibitors in combination with narrowband ultraviolet B (NB-UVB) therapy has shown promise in the

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		UVB) therapy for the treatment of non-segmental vitiligo.	(52 weeks total) Tofacitinib 2 % cream BID 8-16 weeks Tofacitinib 2 % cream BID 24 weeks Delgocitinib cream BID 36 weeks			inhibitors in combination with narrowband ultraviolet B (NB-UVB) therapy for the treatment of non-segmental vitiligo. The authors highlight the recent approval of Opzelura™ (ruxolitinib), a topical JAK inhibitor, by the FDA for the treatment of non-segmental vitiligo.	treatment of non-segmental vitiligo. Topical JAK inhibitors, such as Opzelura™ (ruxolitinib), have been approved by the FDA for the treatment of non-segmental vitiligo.
Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial: a critical appraisal	London, U.K	The objective of the paper was to evaluate the therapeutic efficacy and safety of ruxolitinib cream in the treatment of vitiligo . The study aimed to assess the re-pigmentation effect of ruxolitinib cream by measuring the improvement in Facial Vitiligo Area Scoring Index (F-VASI) and Total Vitiligo Area Scoring Index (T-VASI)	randomly assigned (1:1:1:1:1) to ruxolitinib cream (1·5 % twice daily (BD), 1·5 % daily, 0·5 % daily, or 0·15 % daily) or vehicle (control group) BD. In part two patients in the control group and 0,15 % daily	randomised, controlled, phase 2 trial	150 patients	The study evaluated the therapeutic efficacy and safety of ruxolitinib cream in the treatment of vitiligo Participants were randomly assigned to different concentrations of ruxolitinib cream or a control group A statistically significant proportion of patients who received ruxolitinib cream achieved a 50 % improvement in Facial Vitiligo Area	The study provides evidence for the therapeutic efficacy of ruxolitinib cream in the treatment of vitiligo, a condition for which there is currently no licensed treatment for re-pigmentation. Ruxolitinib cream may offer a new treatment option for patients with vitiligo, potentially leading to improved re-pigmentation of the affected skin. The study highlights the importance of

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						Scoring Index (F-VASI) at week 24 compared to the control group . Improvement in Total Vitiligo Area Scoring Index (T-VASI) was also observed in the ruxolitinib cream group	using standard clinical outcome measures, such as re-pigmentation, adverse events, and preservation of re-pigmentation effect, when conducting trials for interventions in vitiligo The findings of this study may influence future clinical practice and treatment guidelines for vitiligo, as ruxolitinib cream could be considered as a potential treatment option.
Baseline Levels of Circulating Inflammatory Biomarkers Stratify Patients with Vitiligo Who Significantly Repigment after Treatment with Ruxolitinib Cream	United states	The objective of the paper was to characterize the circulating inflammatory biomarker profiles in patients with vitiligo who demonstrated at least 50 % improvement in facial Vitiligo Area Scoring Index (F-VASI) scores after treatment with ruxolitinib cream,	.5 % Ruxolitinib Cream QD (n [15) 1,5 % Ruxolitinib Cream BID (n [15) Total (n [30) 1,5 % Ruxolitinib Cream QD (n [11) 1,5 % Ruxolitinib Cream BID (n [16) Total (n [27)	posthoc analysis of a multicenter, randomized, doubleblind, vehicle-controlled, phase 2	Randomized patients aged 18–75 n = 157	The study analyzed the efficacy of ruxolitinib cream in patients with vitiligo and stratified them based on their improvement in facial Vitiligo Area Scoring Index (F-VASI) scores at week 24. Group 1 (n=30) showed a significant improvement of 79,9 % at week 24 and 91,9 % at week 52, while group 2 (n=27)	This finding has practical implications for personalized treatment approaches in vitiligo, as it suggests that patients with specific inflammatory biomarker profiles may be more likely to respond positively to ruxolitinib cream .

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		compared to those who did not show significant improvement The study aimed to identify potential differences in baseline inflammatory biomarkers between the two groups and determine if these differences could be used to stratify patients and predict therapeutic benefit .				had minimal improvement of 1,1 % and 25,1 % at the respective time points . Proteomic analysis of baseline serum samples revealed 76 differentially expressed proteins between the two groups. Ten proteins were upregulated in group 1, while 64 were elevated in group 2 .	
Drugs targeting the JAK/STAT pathway for the treatment of immune-mediated inflammatory skin diseases: protocol for a scoping review	Spain	The scoping review protocol provides a systematic approach to analyze the available evidence on drugs targeting the JAK/STAT pathway for the treatment of immune-mediated inflammatory skin diseases	-	protocol for systematically conducting a scoping review	patients and or public were not involved in the development of this protocol. The study group developed this study protocol without patient involvement	The scoping review protocol will follow a five-stage approach: identifying the research question, identifying relevant studies, selecting studies, charting the data, and collating, summarizing, and reporting the results. The results will be presented using the PRISMA flow chart and will be organized by topics such as indications,	The methodology outlined in the paper emphasizes the use of evidence derived from well-designed and well-conducted research, promoting reproducibility and reducing the risk of bias . The results of the scoping review will provide unique insights into the indications, mechanisms of action, efficacy, and safety of JAK/STAT pathway-targeting drugs in the

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					mechanism of action, efficacy, safety, and cost.	treatment of dermatological diseases .
The First Live-Cell Based Product in The Iranian Drug List; ReColorCell	Tehran, Iran	The objective of the paper is to highlight the development and registration of ReColorCell® as the first live-cell based product in the Iranian drug list, providing a new treatment option for vitiligo patients in Iran		300 patients	The phase one data published in 2010 on 10 patients and phase three data published in 2018 on 300 patients showed promising results in terms of repigmentation and disease stability in vitiligo patients.	The paper highlights the development and registration of ReColorCell® as the first live-cell based product in the Iranian drug list, providing a new treatment option for vitiligo patients in Iran. The use of cell-based therapies, such as ReColorCell®, has shown promising results in repigmentation and disease stability in vitiligo patients.
Enhancing intradermal delivery of tofacitinib citrate: Comparison between powder-loaded hollow microneedle arrays and dissolving microneedle arrays	UK	The objective of the research was to enhance the intradermal delivery of tofacitinib citrate, a Janus Kinase (JAK) inhibitor used in the treatment of autoimmune skin diseases, by comparing the efficacy of powder-loaded hollow microneedle (MN) arrays and	The study performed a comparison between powder-loaded hollow microneedle (MN) arrays and dissolving MN arrays for the intradermal delivery of tofacitinib citrate. The efficacy of these two types of MN arrays was evaluated in terms		Hollow microneedle (MN) arrays loaded with tofacitinib citrate showed comparable resistance to compression and insertion capabilities to dissolving MN arrays. Hollow MN arrays containing sodium chloride (NaCl) in the formulation led to slightly higher depositions of	The study demonstrates the potential of hollow microneedle (MN) arrays for enhancing the intradermal delivery of tofacitinib citrate, a Janus Kinase (JAK) inhibitor used in the treatment of autoimmune skin diseases. Hollow MN arrays loaded with tofacitinib citrate showed comparable

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	dissolving MN arrays. The study aimed to fabricate hollow MN arrays loaded with tofacitinib citrate and evaluate their efficiency in intradermal drug delivery.	of drug deposition in neonatal porcine skin. Reverse phase high performance liquid chromatography (RP-HPLC) was used to quantify the amount of tofacitinib citrate in samples from in vitro release studies and skin deposition studies A Texture Analyser was used to assess the resistance of MN arrays when pressed against a surface using an axial force, by recording the reduction in height . Full-thickness neonatal porcine skin was used for the evaluation of MN arrays. The skin was placed on tissue paper soaked in PBS pH 7,4 to keep it hydrated .	tofacitinib in the epidermis and dermis of neonatal porcine skin compared to a control cream. However, dissolving MN arrays showed superiority in terms of tofacitinib deposition in the dermis. Control cream and dissolving MN arrays delivered 143,98 µg/cm2 and 835 µg/cm2 of tofacitinib in the dermis, respectively, after 24 hours, confirming the enhanced intradermal drug delivery capacity of MN arrays. The study also developed suitable HPLC methods to quantify tofacitinib citrate in in vitro release studies and in neonatal porcine skin.	resistance to compression and insertion capabilities to dissolving MN arrays, indicating their feasibility as a drug delivery system.

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The results also demonstrated that treatment with ruxolitinib cream continued to show improvements in repigmentation up to week 52, suggesting that this treatment approach may be effective in the long term.[28]

Importantly, the studies also evaluated the use of ruxolitinib cream in different subgroups of patients with vitiligo. It was observed that even the group receiving the lowest concentration of ruxolitinib cream (0,15 % once daily) showed a response rate in F-VASI50 improvement at week 24. This suggests that even at low doses, ruxolitinib cream may have a positive impact in some patients.[29]

In addition, it was observed that patients previously treated with topical steroids or calcineurin inhibitors also responded positively to treatment with ruxolitinib cream, indicating that this approach may be effective in patients who have previously used other treatments.[30,31]

In terms of safety, adverse effects such as application site acne and pruritus were observed in patients who applied ruxolitinib cream for 52 weeks. However, these adverse effects appear manageable and do not preclude ruxolitinib cream from being considered as a potential treatment option.

Comparing these findings with previous research, it can be stated that the results are consistent with previous studies that have investigated the efficacy of Janus kinase (JAK) inhibitors in the treatment of vitiligo. JAKs are a family of enzymes that play an important role in immune response and inflammation, and their inhibition appears to be beneficial in the repigmentation of vitiligo lesions.

Ruxolitinib, in particular, has been shown to be effective in the treatment of vitiligo, and its cream formulation provides a topical administration option that is convenient and well tolerated by patients.[32]

Despite these positive findings, it is important to note some limitations and needs for future research. First, although the results are promising, more long-term and larger patient studies are needed to confirm the efficacy and safety of ruxolitinib cream treatment in vitiligo. In addition, it would be beneficial to further investigate the underlying mechanisms of action of JAKs in the repigmentation of vitiligo lesions.

In conclusion, the results of this systematic review support the efficacy of ruxolitinib cream in the treatment of vitiligo, with significant improvements in repigmentation observed in different patient subgroups. Despite some limitations, these findings are encouraging and suggest that ruxolitinib cream may be an effective and safe treatment option for vitiligo, especially in the context of facial repigmentation. However, more research is needed to confirm these results and to better understand the mechanisms involved in this treatment. This encourages further research in this area and provides hope for patients struggling with vitiligo.

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CONFLICT OF INTEREST

We declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

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