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Topical Ruxolitinib for Treatment of Vitiligo

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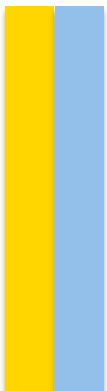

Topical Ruxolitinib for Treatment of Vitiligo

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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Resumo

O vitiligo é um distúrbio crónico autoimune da pigmentação da pele, que cursa com a perda seletiva de melanócitos. O seu processo fisiopatológico permanece em investigação, não sendo ainda totalmente compreendido, conhecendo-se a influência de fatores genéticos, ambientais, bem como de anomalias metabólicas, do stress oxidativo e da adesão celular: o stress ambiental, em combinação com uma predisposição genética, leva a alterações no sistema antioxidante, resultando numa menor adesão dos melanócitos e numa maior suscetibilidade dos mesmos ao stress oxidativo. O vitiligo pode apresentar-se em diferentes tipos, nomeadamente não segmentar e segmentar.

Atualmente, é a doença despigmentante mais comum, afetando cerca de 0.5-2% da população mundial, sendo considerada uma doença estigmatizante e com impacto psicológico não desvalorizável.

Clinicamente, esta patologia manifesta-se por máculas e manchas cutâneas amelanóticas, não descamativas.

Relativamente ao tratamento do vitiligo, é frequentemente utilizada corticoterapia tópica ou sistémica e fototerapia UVB, bem como inibidores da calcineurina. Os corticosteroides diminuem um variado espetro de citocinas, quimiocinas e outros fatores envolvidos nas fases inicial e tardia da resposta imune, suprimindo/reduzindo a atividade das células T. No entanto, não deverão ser utilizados por períodos muito prolongados, devido aos seus efeitos adversos. Já a fototerapia UVB tem também efeito imunomodulador, porém, o seu principal mecanismo de ação é a estimulação da migração e do aumento do espetro de melanócitos, de forma a promover a melanogénese e repigmentação da pele. Além destas modalidades terapêuticas, podem ainda ser usados fármacos inibidores da Janus Quinase (JAK), na sua formulação oral. No entanto, foi recentemente aprovado o uso de ruxolitinib tópico 1.5%. Este fármaco torna possível a repigmentação facial e corporal total de forma significativa. De acordo com estudos recentes, esta terapêutica demonstrou ser geralmente tolerável e eficaz. Alguns dos seus efeitos adversos mais comuns são acne, prurido e esfoliação/descamação, no local da aplicação do creme. Além disso, e à semelhança dos inibidores da JAK administrados por via oral, o uso de ruxolitinib tópico também pode acarretar risco de infeções graves, mortalidade, malignidade, eventos cardiovasculares adversos maiores (MACE) e trombose, embora a incidência destes eventos tenha sido baixa com a aplicação tópica.

Esta revisão bibliográfica tem como objetivo compilar o estado da arte sobre o ruxolitinib. Para isso, foram consultas as bases de dados PubMed, Cochrane e *clinicaltrials.gov*, permitindo a síntese do papel deste fármaco como uma nova opção tópica para o tratamento do vitiligo. Serão abordadas as suas características farmacológicas, bem como os principais resultados de ensaios clínicos publicados. Em última análise, este trabalho visa avaliar a eficácia e segurança da formulação tópica do ruxolitinib.

Palavras chave: Vitiligo; Ruxolitinib; Janus Kinase Inhibitors; JAK-STAT Signaling Pathway; *Topical Administration*; Drug Therapy; Treatment Outcome; Efficacy; Safety

Abstract

Vitiligo is a chronic autoimmune disorder of skin pigmentation that occurs with the selective loss of melanocytes. Its pathophysiological process remains under investigation and is not yet fully understood, but the influence of genetic and environmental factors, as well as metabolic abnormalities, oxidative stress and cell adhesion are known: environmental stress, in combination with a genetic predisposition, leads to alterations in the antioxidant system, resulting in reduced adhesion of melanocytes and their greater susceptibility to oxidative stress.
Vitiligo can come in different types, namely non-segmental and segmental.
It is currently the most common depigmenting disease, affecting around 0.5-2% of the world's population, and is considered a stigmatizing disease with a psychological impact that cannot be underestimated.
Clinically, this condition is manifested by macules and amelanotic, non-squamous skin patches. With regard to the treatment of vitiligo, topical or systemic corticosteroids and UVB phototherapy are often used, as well as calcineurin inhibitors. Corticosteroids reduce a wide range of cytokines, chemokines and other factors involved in the early and late phases of the immune response, suppressing/reducing T-cell activity. However, they should not be used for very long periods due to their adverse effects. UVB phototherapy also has an immunomodulatory effect, but its main mechanism of action is to stimulate the migration and increase the spectrum of melanocytes, in order to promote melanogenesis and skin repigmentation. In addition to these therapeutic modalities, oral Janus Kinase (JAK) inhibitors can also be used. However, the use of topical ruxolitinib 1.5% has recently been approved. This drug makes significant facial and total body repigmentation possible. According to recent studies, this therapy has proved to be generally tolerable and effective. Some of its most common adverse effects are acne, itching and exfoliation/flaking at the site of the cream's application. In addition, and similar to orally administered JAK inhibitors, the use of topical ruxolitinib can also carry a risk of serious infections, mortality, malignancy, major adverse cardiovascular events (MACE) and thrombosis, although the incidence of these events has been low with topical application.
This literature review aims to compile the state of the art on ruxolitinib. To this end, the PubMed, Cochrane and *clinicaltrials.gov* databases were consulted, allowing the role of this drug as a new topical option for the treatment of vitiligo to be summarized. Its pharmacological characteristics will be addressed, as well as the main results of published clinical trials. Ultimately, this work aims to evaluate the efficacy and safety of the topical formulation of ruxolitinib.

Keywords: Vitiligo; Ruxolitinib; Janus Kinase Inhibitors; JAK-STAT Signaling Pathway; *Topical Administration*; Drug Therapy; Treatment Outcome; Efficacy; Safety

List of abbreviations

AUC - area under the concentration-time curve
C_{max} – maximum serum drug concentration
BD – twice daily
BSA – Body Surface Area
CYP – cytochrome
DAMPs - damage-associated molecular patterns
IC_{50} - half-maximal inhibitory concentration
IFN - interferon
IL – interleukin
F-VASI – Facial Vitiligo Area and Severity Index
HSP70 - heat shock protein 70
JAK – Janus Kinase
JAKi – Janus Kinase inhibitors
F-VASI25 - ≥ 25% improvement in Facial Vitiligo Area and Severity Index
F-VASI50 - ≥ 50% improvement in Facial Vitiligo Area and Severity Index
F-VASI75 - ≥ 75% improvement in Facial Vitiligo Area and Severity Index
F-VASI90 - ≥ 90% improvement in Facial Vitiligo Area and Severity Index
NB-UVB – narrowband ultraviolet B
ROS – reactive oxygen species
SD – standard deviation
STATs – signal transducer and activator of transcription
TCI – topical calcineurin inhibitors
TCS – topical corticosteroids
Th – T helper cell
TRM - tissue-resident memory T cells
T-VASI – Total Vitiligo Area and Severity Index
T-VASI25 - ≥ 25% improvement in Total Vitiligo Area and Severity Index
T-VASI50 - ≥ 50% improvement in Total Vitiligo Area and Severity Index
T-VASI75 - ≥ 75% improvement in Total Vitiligo Area and Severity Index
T-VASI90 - ≥ 90% improvement in Total Vitiligo Area and Severity Index
UVA – ultraviolet A
VASI – Vitiligo Area and Severity Index

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Table List

Introduction

Vitiligo is an acquired, chronic immune-mediated skin disease. [1, 2, 10, 13] It is the most common depigmentating disease and affects 0.5 - 2% of the global population without any significant difference in sex, ethnicity, Fitzpatrick skin type or geographic region. [1, 2, 10, 12] The average age of onset is between 10 to 30 years. [13]

It is most frequently classified as either segmental or nonsegmental, with the latter being the more prevalent form and typically categorized based on its anatomical distribution. [1, 13] Nonsegmental vitiligo can develop later in life (when compared to segmental form), it is more likely to present bilaterally, crossing the midline, and is characterized by a slowly progressive and chronic course of depigmentation. In contrast, segmental vitiligo is usually unilateral, rarely crosses the midline, and is marked by rapid onset followed by early disease stabilization. [1, 13]

Well-demarcated white macules and non-scaly patches develop on any part of the body, because of melanocyte destruction. [7, 10, 13] The appearance of these lesions can be particularly stigmatizing and devastating to patients with darker skin phenotypes, due to a bigger contrast with the lighter skin lesions. [13] Some clinical signs of disease activity have been identified: inflammatory borders, the Koebner phenomenon, hypochromic areas/borders and confetti-like depigmentation. [11] It often progresses in flare-ups, with a highly unpredictable long-term course. [2, 11]

Diagnosis is typically direct; however, affected areas are best visualized using a Wood's lamp, which enhances the contrast of amelanotic tissue due to the autofluorescence of underlying dermal collagen. [13] While rarely required, a skin biopsy may be performed to confirm the diagnosis. [13]

Vitiligo has been linked to various autoimmune diseases. [8] The most reported comorbidities include rheumatoid arthritis (RA), alopecia areata (AA), atopic dermatitis (AD), and psoriasis, among others. [8] According to some studies findings, initiation of a JAK inhibitor (JAKi) may contribute to the improvement of concomitant autoimmune conditions. [8] It has also been associated to an important psychosocial burden, significantly affecting patients' quality of life, such as feelings of stigmatization, decreased self-esteem, depression, behavioral alterations, anxiety disorder, social phobia, sleep disorder and cognitive and emotional impairment. [4, 7, 8, 10]

Vitiligo is an autoimmune skin disorder driven by autoreactive CD8+ T cells, leading to melanocyte destruction and depigmentation. [3, 10] Its pathogenesis involves genetic predisposition, oxidative stress, and immune dysregulation. [2, 3] External triggers induce IFN-γ signaling, activating the JAK-STAT pathway and promoting melanocyte apoptosis. [1-3, 7, 8, 10] A self-sustaining inflammatory loop, mediated by CXCL9/CXCL10 and tissue-resident memory T cells (TRMs), drives disease persistence. [2, 7, 10] IL-15 signaling enhances TRM survival and CD8+ T-cell activity, while Treg dysfunction disrupts immune tolerance. [10, 12] Relapses are common post-treatment. [7] Although vitiligo follows a polygenic inheritance pattern, environmental factors play a crucial role in disease progression, mainly without a documented family history. [7]

Vitiligo is an incurable, relapsing disease managed through therapies aimed at stabilizing progression, inducing repigmentation, and improving quality of life. [1, 2, 11] Treatment depends on disease severity and should be initiated as early as possible, with topical corticosteroids or calcineurin inhibitors for localized cases and systemic corticosteroids for widespread, active disease. [1, 2, 10, 11] Narrowband UVB phototherapy is effective, though extremities remain challenging. [2, 11] Laser therapy and cryotherapy are alternatives for small lesions. [1, 2, 11] In stable cases unresponsive to medical treatment, melanocyte transplantation is an option, while extensive vitiligo (>50% BSA)

may require depigmentation with chemical products or even lasers. [11, 13] Given current treatment limitations, developing safer and more effective therapies remains essential. [2, 10]

Ruxolitinib is a selective JAK1/2 inhibitor that disrupts vitiligo pathogenesis by interfering with IFN-γ signaling, inhibiting dendritic cell migration, and reducing cytotoxic T-cell responses, allowing melanocyte recruitment and repigmentation. [1-4, 10]

Its 1.5% cream formulation is the first topical JAKi approved treatment for non-segmental vitiligo in several countries, based on phase III TRuE-V trials. [1-3, 5, 10] It is indicated for patients ≥12 years with uncontrolled disease, applied twice daily to affected areas (≤10% BSA). [1, 2] Facial lesions show early responses, with repigmentation visible within four weeks. [8] Treatment may continue beyond 24 weeks, but discontinuation is advised in the EU and UK if repigmentation remains <25% after 52 weeks. [1] Disease duration or baseline activity may not predict response. [8]

Objectives

This article aims to review the role of Topical Ruxolitinib in the treatment of Vitiligo.

Methods

The current state of the field was evaluated through a literature search using the PubMed and Cochrane databases, as well as ClinicalTrials.gov, up to December 2024. The search strategy involved combinations of the following medical terms: "Vitiligo," "Topical," and "Ruxolitinib". The articles selected met the inclusion criteria, namely: patients with a confirmed diagnosis of vitiligo, evaluating the administration of ruxolitinib, either as monotherapy or in combination with conventional therapies. conventional therapies. Studies were considered that address efficacy, assessed through repigmentation or indices such as VASI, and the safety of the treatment, considering local or systemic adverse effects. Eligible studies included randomized clinical trials, observational studies, narrative reviews, systematic reviews and meta-analyses. reviews. Articles were excluded when they did not involve patients with confirmed vitiligo or if they did not directly analyze ruxolitinib, as well as those that did not make comparisons with conventional therapies. We also excluded studies that did not present data on the efficacy or safety of ruxolitinib, as well as pre-clinical studies, letters to the editor, editorials, opinions or isolated case reports. Articles published in languages other than mentioned, or dated before 2014, were not included. After applying the exclusion criteria, 25 articles and clinical trials were used as outlined in the References.

Discussion

Pathogenesis of Vitiligo

Vitiligo is a complex autoimmune skin disorder characterized by the progressive loss of melanocytes, primarily driven by autoreactive CD8+ cytotoxic T cells, leading to depigmented macules. [3, 10] Its pathogenesis is still unclear and probably multifactorial, involving environmental factors, genetic predisposition, oxidative stress and immune dysregulation. [2, 3]

The onset of vitiligo is often associated with external oxidative stressors (including UV radiation, chemical exposure, and trauma), leading melanocytes to release reactive oxygen species (ROS), heat shock protein 70 (HSP70), and damage-associated molecular patterns (DAMPs). [10] The accumulation of these molecules leads to melanocyte dysfunction and increased antigen presentation, activating innate immune system and initiating a cascade of immune responses. [10] Autoreactive CD8+ T lymphocytes become activated, producing interferon-gamma (IFN-γ). [1, 10] The binding of IFN-γ, a key regulator in vitiligo, to its receptor activates the Janus kinase (JAK)-signal transducer (particularly in vitiligo, JAK 1 and 2) and activator of transcription (STAT) pathway. [7, 10] In other words, IFN-γ binds to its cell surface receptor, triggering the activation of the transmembrane protein kinase JAK, which undergoes self-phosphorylation; this event leads to the phosphorylation and dimerization of signal transducers and activators of transcription (STATs), thereby activating the JAK-STAT pathway through JAK1/2 signaling. [8] The subsequent initiation of gene transcription drives the autoimmune response, ultimately leading to melanocyte apoptosis, cellular senescence and depigmentation. [3, 8] This activation stimulates keratinocytes to release chemokines CXCL9 and CXCL10, which recruit additional immune cells via CXCR3 chemokine receptor. [2, 10] This establishes a self-sustaining positive feedback loop that drives disease progression. [7, 10]

Relapse often occurs during the first year after treatment discontinuation, mainly at the same areas that were previously affected. [7] Tissue-resident memory T cells (Trms) play a key role in the persistence and recurrence of vitiligo through IL-15-dependent survival signaling: IL-15 promotes the recruitment and proliferation of cytotoxic CD8+ T cells. [10] Moreover, elevated IL-15 levels have been observed in the sera of vitiligo patients, with a positive correlation to disease severity. [10, 12] During relapse or flare-up, oxidative stress stimulates keratinocytes to produce IL-15 and its membrane-bound receptor IL-15Rα. [10] This activation promotes survival, maturation and cytotoxic function of TRMs through a mechanism involving JAK1 and JAK3 and the subsequent STAT3 and STAT5 phosphorylation. [10, 12] Meanwhile, regulatory T cells (Tregs) are critical for maintaining self-tolerance by suppressing autoreactive CD8+ T cell activity, a process supported by IL-2 signaling. [10] Therefore, a functional impairment or reduced number of Tregs in vitiligo contributes to the breakdown of immune tolerance, allowing autoreactive CD8+ T cells to persist and attack melanocytes. [10]

From a genetic perspective, vitiligo follows a polygenic inheritance pattern, with individual genetic factors contributing only modestly to disease susceptibility. [7] Notably, more than 90% of cases occur without a documented family history. [7]

Current vitiligo treatment

Vitiligo is an incurable disease that evolves in flare-ups, but there are several treatment options aimed at stabilizing active disease, preventing flare-ups, halting disease progression, inducing

repigmentation, melanocyte regeneration and proliferation, as well as improving the QoL of these patients. [1, 2, 11]

Although the European and British guidelines are based on the activity and severity of the disease, treatment must be chosen on a case-by-case basis. [2] In addition, pharmaceutical management should be started as early as possible, as repigmentation largely depends on the affected body areas and the extent of depigmentation. [1, 11] It should be noted that almost 50% of vitiligo lesions recur in the first year after repigmentation without maintenance therapy: for example, clinical studies have shown that the application of tacrolimus 0.1% twice weekly, independent of sun exposure, reduces the relapse rate in facial treatment from 40% to 9.7%. [11]

In case of localized disease, the first line therapies usually include the once-daily use of topical corticosteroids (TCS) or twice-daily use of topical calcineurin inhibitors (TCI), while in rapidly progressing cases with unstable, widespread or recalcitrant vitiligo, systemic treatment with oral or intramuscular corticosteroids (for example, systemic corticosteroids for up to 6 months). [1, 2, 10, 11]

TCI are a good alternative to TCS in adults and children, considering their better safety profile, especially in relation to the risk of skin atrophy, but they must be discontinued in case of superficial skin infections, malignancies (particularly lymphomas), immunosuppression, extensive sun exposure or application site burning. [2, 13]

Phototherapy with narrowband ultraviolet B (NB-UBV) can be used, either alone or in combination with other treatments, to promote repigmentation, and it may be administered twice to three times a week, as long as there is ongoing repigmentation. [2] UVB should be preferred to UVA. [11] Nevertheless, it is well known that extremities are difficult to treat. [2] The most common acute adverse effect is skin type- and dose-dependent erythema that usually happens 12 to 24 hours after irradiation. [2] This therapy is not related to an increased risk of skin cancer (up to at least 400 sessions). [11]

Laser therapy is an effective and safe treatment option for vitiligo. However, its use remains restricted due to its high cost and applicability only to small, affected areas. [2] For small areas, cryotherapy is also an interesting option. [1, 11]

Depending on the season (especially during summer), moderate but regular sun exposure is recommended to stimulate repigmentation. [11] This should be done at least three to four times per week without sunscreen, until the skin develops a pink hue. It is important to note that individuals with vitiligo have a lower risk of developing skin cancer, particularly melanoma. [11]

Transplants are another possible therapy, and they can be proposed after the failure of medical treatments for vitiligo that has been stable for at least 12 months and segmental vitiligo. [11, 13] There are several techniques described, but the preferred one is epidermal suspensions. [11]

Depigmentation may be considered for patients with depigmented areas affecting more than 50% of the body surface area (BSA), using chemical products (such as MEBH - hydroquinone monobenzylether, or depigmenting lasers). [11, 13]

However, considering the limited efficacy and potential side effects of existing treatments, as well as the unmet need to enhance patients' quality of life, the development of new safe and effective therapeutic options is essential. [2, 10]

The role of JAK-STAT pathway

Janus kinase proteins were historically named after the Roman god Janus, symbolizing gateways, due to their intracellular association with membrane receptors and their role in signal transduction. [6]

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway is a critical intracellular signaling cascade that regulates gene expression in response to cytokines, growth factors and hormones, playing a key role in immune function and cellular homeostasis. [3, 9, 12] The JAK family includes four members [JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2)], while the STAT family consists of seven protein members (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6). [3, 8, 9]

JAKs are enzymes belonging to the tyrosine kinase family, associated with the intracellular domains of type I and type II cytokine receptors. [3, 8] Type I receptors interact with various interleukins, colony-stimulating factors, and hormones such as erythropoietin, prolactin, and growth hormone, while type II receptors primarily bind proinflammatory interferons and cytokines. [6, 8] JAKs play a pivotal role in transmitting signals initiated by cytokine-receptor interactions at the cell membrane, thereby regulating cellular processes and immune cell function. [8] Upon cytokine or growth factor binding to specific membrane receptors, receptor dimerization is induced, bringing two JAKs into close proximity, facilitating their transphosphorylation and subsequent activation. [3, 8, 9, 12] In response, STAT proteins, which reside in the cytoplasm, bind to phosphorylated receptors, undergo phosphorylation, dimerize, and translocate into the nucleus to drive the transcription of target genes involved in various cellular responses. [2, 3, 8, 9, 13]

JAK proteins form specific functional pairings, with JAK1 capable of associating with JAK2 or JAK3, while JAK2 can form homodimers. [8, 9] These pairings dictate downstream intracellular signaling cascades, ultimately modulating distinct biological responses. [3, 8, 9] For example, JAK1 and JAK2 are mediators of cytokine and growth factor signaling, being involved in the processes of haematopoiesis and immunity, and act downstream of IFN signaling. [1] The JAK2 V617F mutation is closely linked to myeloproliferative neoplasms (MPNs), such as myelofibrosis, polycythemia vera, and essential thrombocythemia. It is detected in almost 100% of patients with polycythemia vera and in more than 75% of those with essential thrombocythemia. [12]

Since dysregulation of the JAK-STAT pathway is implicated in various autoimmune and inflammatory skin disorders, Janus kinase inhibitors (JAKi) are designed to selectively target the adenosine triphosphate (ATP) binding pocket of JAKs. [8, 9] By blocking ATP binding, JAKi prevent the phosphorylation and activation of STATs, thereby reducing JAK-STAT signaling and mitigating the inflammatory response. [3, 8, 9]

A JAKi is often effective across multiple diseases that share the same JAK isoform. However, due to the overlapping and nonspecific nature of JAK selectivity, a single JAKi may also target signaling pathways associated with different JAK isoforms, potentially leading to broader immunomodulatory effects. [3, 6] For example, in the IFN-γ signaling pathway, a key cytokine implicated in vitiligo pathogenesis, IFN-γ exerts its effects through IFN-γ receptors 1 and 2, utilizing JAK1 and JAK2 as intracellular kinases and STAT1 and STAT2 as downstream substrates. [3] While IFN-γ signaling can be effectively inhibited by targeting JAK1 or JAK2 (namely JAKi in the treatment of non-segmental vitiligo), it is important to acknowledge that these JAK proteins are shared by multiple cytokines and growth factors, which may lead to off-target effects. [1, 3] Recently developed JAK1-selective small interfering RNA (siRNA) inhibitors provide absolute specificity for the JAK1

subtype; however, they still inhibit multiple cytokines that rely on JAK1 for signaling. [3] Another crucial cytokine involved in vitiligo, IL-15, primarily signals through JAK3, which is utilized by fewer cytokines compared to JAK1 and JAK2. [3] Nevertheless, even the development of a highly specific JAK3 inhibitor would inadvertently suppress essential cytokine signaling pathways, including those of IL-2 and IL-4, potentially leading to unintended immunomodulatory effects. [3]

Although most JAKi have shared chemical structure of pyrrolopyrimidine skeleton, the inhibitory properties are different, depending on the bioavailability determined by administration routes, such as oral versus topical: JAKi can work rapidly within hours in a topical formulation and within days in oral formulation. [3, 6]

Adverse effects of JAKi

Systemic JAKi with enhanced selectivity may offer an improved safety profile. [8] However, this selectivity presents challenges due to the complex network of cytokine interactions and the ubiquitous role of JAK-STAT signaling in both immune and nonimmune cells. [8] While greater specificity may expand therapeutic applications across various diseases, it could also inadvertently lead to unexpected off-target effects. [8]

Treatment with JAKi may also affect the function of T and B lymphocytes and natural killer cells. [3, 8] This condition leads to a possible onset or worsening of infectious diseases such as reactivation of Herpes Zoster virus and upper respiratory tract infections (namely, pneumonia). [3, 8] This therapy can also cause elevated blood cholesterol levels (even though this rise has not been associated to an increased cardiovascular disease risk) and elevated serum creatinine or liver transaminase levels in older patients. [8, 13] Additionally, it can also lead to hematopoietic disorders (such as thrombocytopenia, anemia and neutropenia) and to development of thromboses, malignant lymphomas and solid tumors. [3, 13]

Thus, prior to treatment with systemic JAKi, it is recommended to perform complete and differential blood counts, renal and liver function panel, and baseline lipid panel as well as hepatitis B and C, tuberculosis testing (to exclude latent or active tuberculosis), and screening for HIV. [6, 8]

There is lack of data concerning the treatment of pregnant women with JAKi, so these patients' management during conception, pregnancy, lactation is challenging, because there are no large clinical studies on their effects on these women and even on the fetus and newborns. [6]

Topical application is preferable to systemic administration, because it provides localized benefits and mitigate off-target systemic effects. [3, 8] The most common adverse effect related to this new administration route is acneiform eruptions and transient acne, according to several studies, although the pathogenesis of acne in this context is still unknown. [4, 8] In a particular case, during a 52-week study using delgocitinib 0,5% ointment, 69% of patients had some adverse effects (mild and unrelated to delgocitinib): the most common was nasopharyngitis, followed by acne, contact dermatitis and folliculitis at the application site. [3] The adverse effects related to topical ruxolitinib will be explored in another section of the present review.

Ruxolitinib

Ruxolitinib is a potent and selective JAK1 and JAK2 inhibitor. [1, 2] In addition to interfering with IFN-γ and its downstream signaling pathways, ruxolitinib has been shown to inhibit the differentiation

and migratory capacity of dendritic cells (DCs) in vivo. [3, 10] This inhibition reduces the induction of cytotoxic T-cell responses and antigen-specific T-cell responses, both of which play a critical role in the pathogenesis of vitiligo. [10] Ultimately, JAK inhibition with ruxolitinib cream disrupts vitiligo pathogenesis and allows time for melanocyte recruitment and repigmentation. [4]

Ruxolitinib, in its topical formulation (1,5% cream), is the first topical JAKi to be approved in several countries (including the USA, the UK and those of the EU; it was the second in Japan, following delgocitinib) to treat non-segmental vitiligo, based on data from the two phase III TruE-V clinical trials. [1-3, 5, 10] It was approved by FDA in July 2022 to treat vitiligo and, previously, in September 2021, to treat atopic dermatitis. [5]

Topical ruxolitinib was approved for the treatment of non-segmental vitiligo in non-immunocompromised aged ≥ 12 years whose disease is uncontrolled by topical prescription therapies, or when these are not advisable/recommended. [1, 2] The recommended dose of ruxolitinib cream for the treatment of vitiligo is the application of a thin layer of cream to depigmented areas (avoiding the lips to prevent ingestion) twice daily (minimum 8h between each administration), covering up to 10% of the total body surface area (BSA). [1, 2] This dosage resulted in more pronounced repigmentation in facial lesions, with observable responses as early as four weeks. [8] The maximum recommended usage of ruxolitinib cream varies by body region, with patients advised not to exceed one 60 g tube per week or two 100 g tubes per month. [1] While treatment may be required for more than 24 weeks, discontinuation should be considered in the EU and UK if less than 25% repigmentation is achieved in the affected areas after 52 weeks of therapy. [1] The duration of the disease or its activity at baseline may not be a determining factor in the treatment response. [8]

Other alternative names to this therapy are Opzelura® or INCB018424 and its chemical name is (R)-3-(4-(7H-pyrrolo[2,3-d]pymiridin-4-yl)-1H-pyrazol-1-yl)-3cyclopentylpropanenitrile phosphate. [2] Opzelura® (OPZ) is a white to off-white, oil-in-water, solubilized emulsion containing 1,5% ruxolitinib phosphate and a various number of other ingredients, including propylene glycol, methylparaben, propylparaben, xanthan gum, light mineral oil, glyceryl stearate, polysorbate 20, petrolatum white, cetyl alcohol, stearyl alcohol, dimethicone 360, medium-chain triglycerides, edetate disodium, polyethylene glycol 200, phenoxyethanol and water. [2, 12] Some warnings and precautions include serious infections, non-melanoma skin cancer, thrombosis, thrombocytopenia, anaemia and neutropenia. [2]

As far as oral ruxolitinib is concerned, it was approved earlier by FDA and EMA, in order to treat primary myelofibrosis, polycythaemia vera and acute graft-versus-host disease. [2, 10] A limited number of case reports suggest a potential role for oral ruxolitinib in the treatment of vitiligo. [2] However, pigmentation has been observed to regress upon discontinuation of therapy, even in cases where near-complete facial repigmentation was achieved. [2, 8]

Pharmacodynamics and Pharmacokinetics

Since ruxolitinib cream is an inhibitor of JAK1 and JAK2, and subsequently of JAK-STAT pathway, it leads to a diminished chemokines level such as CXCL10, to a reduced tissue inflammation, and consequently lessens the extent of skin depigmentation. [1] Preclinical studies using cellular assays and animal models demonstrated that ruxolitinib has a half-maximal inhibitory concentration (IC_{50}) of <100 nM. [1] As shown in table 1, Ruxolitinib demonstrates selectivity for JAK1 and JAK2 based on its IC50 but functions as a pan-JAK inhibitor at low concentrations, as indicated by its inhibition

constant (Ki) value. [3] IC50 is highly variable, influenced by ATP levels, JAK concentration, and assay conditions, making cross-study comparisons unreliable. [3] In contrast, Ki, which reflects inhibitor dissociation, is more stable but still affected by receptor binding, pH, and temperature. [3]

In vivo, topical application of ruxolitinib 1.5% cream twice daily resulted in minimal systemic exposure (with a plasma concentration only approximately one-thirtieth) while achieving higher epidermal and dermal concentrations (with a steady-state epidermal concentration nearly 2000-fold higher) and leaving other organs unaffected, compared to oral administration. [1, 2, 3, 12] Due to the low systemic exposure following topical administration, the likelihood of drug–drug interactions is minimal. [1] This topical formulation effectively inhibited JAK-STAT signaling in the dermis for a prolonged period, optimizing efficacy while minimizing potential systemic adverse effects associated with JAK inhibition. [1, 2, 12] For effective dermal distribution, a drug must have (a) sufficient solubility (to achieve high enough concentrations to facilitate the first-order diffusion) and (b) permeability to cross the stratum corneum, and (c) an optimal balance to transition from the epidermis to the dermis. [12] These 3 properties are crucial for achieving active skin concentration. [12] Ruxolitinib meets these criteria, proving effectiveness in its topical formulation. [12]

In an open-label, proof-of-concept phase II trial, 11 adults with vitiligo received topical ruxolitinib 1.5% cream twice daily for 20 weeks, demonstrating significant repigmentation of facial lesions. [1] Similar findings were observed in a randomized, double-blind, dose-ranging, multicenter phase II trial involving 157 patients, where ruxolitinib cream (1.5% twice daily, 1.5% once daily, 0.5% once daily, or 0.15% once daily) was applied for 24 weeks. [1] These repigmentation effects were sustained up to week 156 with continued open-label treatment. [1]

Short-term stability studies demonstrated that the emulsion exhibited good physical stability, with no evidence of chemical instability. These findings were further corroborated by longer-term stability studies. [12]

The pharmacokinetics of topical ruxolitinib were evaluated in 429 patients aged ≥12 years with vitiligo who applied ruxolitinib cream to the same skin areas twice daily for 24 weeks. [1] The mean steady-state through plasma concentration of ruxolitinib was 56.9 nM, and the projected area under the concentration-time curve from 0 to 12 hours ($AUC_{0–12}h$) was 683 h·nM, while in patients with renal impairment, the estimated AUC was approximately two-fold higher. [1] In both TRuE-V trials, plasma ruxolitinib concentrations were also comparable between the two trials, with mean (±SD) steady-state levels averaging 55.8±56.7 nM in TRuE-V1 and 58.0±68.1 nM in TRuE-V2 between weeks 4 and 24. [4] The mean topical bioavailability of ruxolitinib was 9.7%. [1] In vitro data indicate that ruxolitinib is 97% bound to plasma proteins, primarily albumin. [1] The mean elimination half-life of topical ruxolitinib was approximately 3 hours. [1, 12] Ruxolitinib is primarily metabolized by and is a substrate of cytochrome P450 (CYP) 3A4. [1] As such, CYP3A4 inhibitors may increase systemic ruxolitinib levels, potentially raising the risk of adverse effects, while CYP3A4 inducers may reduce its concentrations. [1] Topical ruxolitinib is not expected to inhibit or induce major CYP enzymes, nor affect P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), or the principal organic anion transporters (OAT). [1]

Efficacy

The efficacy of Ruxolitinib cream in patients with vitiligo was assessed in several clinical trials, as presented below.

Starting with an open label, phase II, proof-of-concept pilot trial (NCT02809976) (Table I), it was the first study assessing whether topical ruxolitinib 1.5% would be able to induce repigmentation in vitiligo lesions. The study population consisted of 11 adult patients aged 18 to 65 years. However, only 9 patients completed the trial: one patient was lost to follow-up, while another voluntarily withdrew from the study. Ruxolitinib 1.5% phosphate cream was applied twice daily for 20 weeks to all the affected areas with vitiligo. The efficacy was evaluated by comparing the percent change in VASI, BSA, VEFT – BSA, VEFT – Disease staging and progression, the number of subjects who achieved PGVA of Clear or Almost Clear, and the mean DLQI scores, on baseline and week 20. On week 20, eleven participants had a mean percent change in VASI of 23% (95% CI 4 to 43%) and a mean percent change in BSA of 11.2% (SD: 26.4%). Additionally, on week 20, 2 participants (18.2%) achieved a PGVA of clear or almost clear. With regard to the mean DLI scores at week 20, 11 participants obtained a mean score of 3 (SD: 3.46) on a scale, compared with a mean of 2.9 (SD: 2.67) on baseline. Regarding the mean of percent change in VEFT – Disease staging on week 20, 11 participants achieved a mean percent change of 4.5% (SD: 2.4%). Ultimately, 11 participants had a mean percent change in VEFT – Disease Progression of -0.5% (SD:1.1%) on week 20. So all these results demonstrate that patients achieved an improvement in repigmentation and milder forms of the disease with this treatment. [2, 20]

A phase II, randomized, double-blind, dose-ranging study (NCT03099304) (Table I) was conducted with the purpose of evaluating the efficacy, safety and tolerability of ruxolitinib cream in patients with vitiligo. It involved 157 participants aged 18 to 75 years (all having vitiligo involving <20% of their baseline total BSA) who were randomized to receive one of four different doses of topical ruxolitinib (1.5% twice daily, 1.5% once daily, 0.5% once daily, 0.15% once daily) or vehicle (1:1:1:1:1). The participants were followed for 52 weeks and there was no restriction on the area of application of ruxolitinib cream. There was also a 104-week open-label extension period when topical ruxolitinib was combined with NB-UVB. After 24 and 52 weeks of treatment, a greater proportion of patients who received ruxolitinib cream demonstrated improvements in F-VASI scores of ≥50% (F-VASI50), ≥75% (F-VASI75), and ≥90% (F-VASI90) compared to those who received the vehicle. Specifically, among patients treated with 1.5% ruxolitinib cream twice daily, 45% and 58% achieved F-VASI50 at weeks 24 and 52, respectively. Additionally, 30% and 52% achieved F-VASI75 at weeks 24 and 52, respectively, while 33% attained F-VASI90 at week 52. Total VASI50 (T-VASI50) responses were observed in a dose-dependent manner, with 20% of patients receiving 1.5% ruxolitinib cream twice daily achieving T-VASI50 at week 24, increasing to 45% at week 52. A descriptive subgroup analysis did not reveal significant differences in response rates based on race, skin type, disease status, or total body surface area affected (T-BSA). However, among patients receiving 1.5% ruxolitinib cream twice daily, those who achieved F-VASI50 by week 24 were more frequently female (60.0% vs. 33.3%) and aged ≤50 years (58.8% vs. 31.3%). Furthermore, patients with previously treated vitiligo refractory to phototherapy, corticosteroids, and topical calcineurin inhibitors also achieved F-VASI50. At week 52, T-VASI50 achievement with twice-daily 1.5% ruxolitinib treatment was most commonly observed in patients with facial vitiligo, while response rates were lower among those with upper or lower limb involvement (60% vs. 52.9% and 52.6%, respectively). The lowest response rates were observed among patients with vitiligo affecting hands or feet, with 15.0% and 29.4% achieving T-VASI50, respectively. During the open-label phase beginning at week 104, optional concomitant NB-UVB therapy was permitted at different frequencies across different study centers. Among the 19 patients who received 12 weeks of NB-

UVB therapy, the combination was well tolerated and resulted in improved repigmentation of both face and total body. [2, 9, 10, 21]

A phase II, interventional (NCT05247489) (Table I) was conducted with the purpose of evaluating the efficacy and safety of ruxolitinib cream with or without phototherapy in adolescent and adult patients with non-segmental vitiligo. It involved 55 participants, all having vitiligo involving <10% of their baseline total BSA: 20 received ruxolitinib 1.5% cream BD and 35 received ruxolitinib 1.5% cream BD combined with NB-UVB. Change from baseline in T-VASI at week 48 was evaluated in both groups: -3.43 score on a scale (SD:1.219) in 6 participants receiving only ruxolitinib 1.5% cream BD and -3.46 score on a scale (SD: 2.106) in 26 participants receiving ruxolitinib 1.5% cream BD associated with NB-UVB. In 6 patients receiving only ruxolitinib 1.5% cream BD, 100% (95% CI 54.1 to 100%) achieved F-VASI50 at week 48 and, in 26 participants receiving ruxolitinib 1.5% cream BD associated with NB-UVB, 96.2% (95% CI 80.4 to 99.9%) achieved F-VASI50 at week 48. In 6 patients receiving only ruxolitinib 1.5% cream BD, 100% (95% CI 54.1 to 100%) achieved F-VASI75 at week 48 and, in 26 participants receiving ruxolitinib 1.5% cream BD associated with NB-UVB, 84.6% (95% CI 65.1 to 95.6%) achieved F-VASI75 at week 48. In 6 patients receiving only ruxolitinib 1.5% cream BD, 66.7% (95% CI 22.3 to 95.7%) achieved F-VASI90 at week 48 and, in 26 participants receiving ruxolitinib 1.5% cream BD associated with NB-UVB, 53.8% (95% CI 33.4 to 73.4%) achieved F-VASI90 at week 48. In 6 patients receiving only ruxolitinib 1.5% cream BD, 83.3% (95% CI 35.9 to 99.6%) achieved T-VASI50 at week 48 and, in 26 participants receiving ruxolitinib 1.5% cream BD associated with NB-UVB, 57.7% (95% CI 36.9 to 76.6%) achieved T-VASI50 at week 48. In 6 patients receiving only ruxolitinib 1.5% cream BD, 50% (95% CI 11.8 to 88.2%) achieved T-VASI75 at week 48 and, in 26 participants receiving ruxolitinib 1.5% cream BD associated with NB-UVB, 19.2% (95% CI 6.6 to 39.4%) achieved T-VASI75 at week 48. In 6 patients receiving only ruxolitinib 1.5% cream BD, 16.7% (95% CI 0.4 to 64.1%) achieved T-VASI90 at week 48 and, in 26 participants receiving ruxolitinib 1.5% cream BD associated with NB-UVB, 7.7% (95% CI 0.9 to 25.1%) achieved T-VASI90 at week 48. In 6 patients receiving only ruxolitinib 1.5% cream BD, there was a -78.06% (SD: 20.018) change in F-BSA at week 48 and, in 26 participants receiving ruxolitinib 1.5% cream BD associated with NB-UVB, there was a -60.51% (SD: 29.172) change in F-BSA at week 48. In 6 patients receiving only ruxolitinib 1.5% cream BD, there was a -47.03% (SD: 29.37) change in T-BSA at week 48 and, in 26 participants receiving ruxolitinib 1.5% cream BD associated with NB-UVB, there was a -27.3% (SD: 30.712) change in T-BSA at week 48. So, results demonstrate that treatment with ruxolitinib 1.5% cream BD is more effective than treatment with ruxolitinib 1.5% cream BD combined with NB-UVB. [22]

Two multinational, phase III, double-blind, randomized, vehicle-controlled clinical trials were conducted to explore the efficacy and safety of ruxolitinib 1.5% cream for the treatment of vitiligo. TRuE-V1 (NCT04052425) (Table I) included 330 patients and TRuE-V2 (NCT04057573) (Table I) included 344 patients, all of them aged >12 years with non-segmental vitiligo involving ≤ 10% of their T-BSA, including ≥ 0.5% BSA on facial areas and ≥ 3% on non-facial areas. Participants were randomly assigned in a 2:1 ratio to apply either 1.5% ruxolitinib cream or a matching vehicle twice daily to all depigmented vitiligo lesions for 24 weeks. This was followed by an additional 28-week period during which all participants applied 1.5% ruxolitinib cream twice daily. Regarding TRuE-V1, at week 24, the percentage of participants who reached F-VASI75 with 1.5% ruxolitinib cream was 29.8% and with vehicle was 7.4%; the percentage of participants who reached F-VASI25 was 69.8% and 30%, respectively; the percentage of participants who reached F-VASI50 was 51.2% and 16.9%, respectively; the percentage of participants who reached F-VASI90 was 15.3% and 2.2%, respectively; the percentage of participants who reached T-VASI25 was 48.8% and 23.8%,

respectively; the percentage of participants who reached T-VASI50 was 20.6% and 5.1%, respectively; the percentage of participants who reached T-VASI75 was 4.1% and 1.8%, respectively; the percentage of participants who reached T-VASI90 was 0.5% and 0%, respectively; the percentage of participants who reached VNS of 4 or 5 was 24.5% and 3.3%, respectively. At the end of this 24-week period, there was an extension period of 28 weeks, during which the group previously treated with topical ruxolitinib continued the same treatment (1.5% ruxolitinib cream BD) and the other group, previously receiving matching vehicle, started being treated with 1.5% ruxolitinib cream BD. This way, at week 52, in the group of participants who had previously been treated with topical ruxolitinib (and continued receiving the same treatment), 89.6% of them reached F-VASI25, 75.1% reached F-VASI50, 52.6% achieved F-VASI75, 32.9% achieved F-VASI90, 77.5% reached T-VASI25, 53.2% achieved T-VASI50, 20.2% reached T-VASI75 and finally 3.5% achieved T-VASI90; in turn, in the group that previously received matching vehicle (and started receiving topical ruxolitinib), 74.4% achieved F-VASI25, 56.1% reached F-VASI50, 26.8% achieved F-VASI75, 12.2% reached F-VASI90, 56.1% achieved T-VASI25, 31.7% reached T-VASI50, 9.8% achieved T-VASI75 and, ultimately, 2.4% achieved T-VASI90. These results demonstrated that continuous treatment with 1.5% ruxolitinib cream is more effective and beneficial than using a matching vehicle. Regarding TRuE-V2, at week 24, the percentage of participants who reached F-VASI75 with 1.5% ruxolitinib cream was 30.9% and with vehicle was 11.4%; the percentage of participants who reached F-VASI25 was 63.9% and 32%, respectively; the percentage of participants who reached F-VASI50 was 51.4% and 20.9%, respectively; the percentage of participants who reached F-VASI90 was 16.3% and 1.3%, respectively; the percentage of participants who reached T-VASI25 was 50.2% and 21.2%, respectively; the percentage of participants who reached T-VASI50 was 23.9% and 6.8%, respectively; the percentage of participants who reached T-VASI75 was 8% and 1.8%, respectively; the percentage of participants who reached T-VASI90 was 1% and 0%, respectively; the percentage of participants who reached VNS of 4 or 5 was 20.5% and 4.9%, respectively. At the end of this 24-week period, there was an extension period of 28 weeks, during which the group previously treated with topical ruxolitinib continued the same treatment (1.5% ruxolitinib cream BD) and the other group, previously receiving matching vehicle, started being treated with 1.5% ruxolitinib cream BD. This way, at week 52, in the group of participants who had previously been treated with topical ruxolitinib (and continued receiving the same treatment), 82.5% of them reached F-VASI25, 74% reached F-VASI50, 48% achieved F-VASI75, 27.7% achieved F-VASI90, 76.8% reached T-VASI25, 49.2% achieved T-VASI50, 20.9% reached T-VASI75 and finally 6.8% achieved T-VASI90; in turn, in the group that previously received matching vehicle (and started receiving topical ruxolitinib), 71.6% achieved F-VASI25, 49.4% reached F-VASI50, 29.6% achieved F-VASI75, 16% reached F-VASI90, 53.1% achieved T-VASI25, 22.2% reached T-VASI50, 8.6% achieved T-VASI75 and, ultimately, 1.2% achieved T-VASI90. These results demonstrated that continuous treatment with 1.5% ruxolitinib cream is more effective and beneficial than using a matching vehicle. Additionally, these results were very similar to those obtained in TRuE-V1. [1-4, 7, 9-11, 14, 15, 23, 24]

Ultimately, a phase III, double-blind, vehicle-controlled, randomized withdrawal and treatment extension study (NCT04530344) (Table I) was conducted to assess the duration of response following withdrawal of ruxolitinib cream (Cohort A vehicle group), safety and maintenance of response with continued use of ruxolitinib cream in participants who completed either TRuE-V1 or TRuE-V2. It involved 458 participants (adolescents and adults aged >12years) with non-segmental vitiligo and BSA ≤ 10%. Among patients who showed no facial repigmentation at week 24 of both TRuE-V clinical trials, improvements in F-VASI were observed in 97.1% of patients at week 104.

Among those with limited facial repigmentation at week 24, improvements in F-VASI at week 104 were observed in 83.3% of patients. Across both groups (with no facial repigmentation or with limited repigmentation in that area), 54.9% of patients achieved a ≥75% improvement from baseline in F-VASI (F-VASI75) by week 104. Among patients with no body repigmentation at week 24, improvements in T-VASI were observed in 93.3% of patients at week 104. For those with limited body repigmentation at week 24, improvements in T-VASI at week 104 were observed in 81.6% of patients. Across both groups with <25% total body repigmentation at week 24, 50.0% of patients achieved a ≥50% improvement in T-VASI (T-VASI50) by week 104. In conclusion, in both TRuE-V studies, continued application of ruxolitinib cream for an additional 80 weeks resulted in enhanced repigmentation among patients with nonsegmental vitiligo who had achieved limited or no repigmentation by week 24. These two-year findings from the TRuE-V studies underscore the importance of prolonged treatment in patients with vitiligo, even when minimal or no repigmentation is observed after six months of therapy. [10, 25]

Facial epidermis' reduced thickness enhances topical absorption, further potentiated by sun exposure. Additionally, a higher follicular density on the face promotes greater repigmentation compared to the hands and feet. [8, 13]

In addition to the studies described above, there are some that are to be developed and others that are already in progress. A phase 3, randomized, double-blind study (NCT06804811) is scheduled to start on 08th August 2025 and end on 01st December 2027, involving around 250 participants (but not yet to be recruited); it will aim to assess the efficacy and safety of ruxolitinib cream in children with non-segmental vitiligo, aged between 6 and 12 years; the intervention will be carried out using ruxolitinib cream and vehicle cream. [16] Another phase 3, randomized, double-blind study (NCT06548360) started on 24th January 2025 and is expected to end on 13th March 2027, with around 180 participants being recruited; it aims to assess the efficacy and safety of ruxolitinib cream in pediatric patients with non-segmental vitiligo; the intervention is being carried out using ruxolitinib cream and vehicle cream. [17] There is also a prospective, open-label, single-center, split face randomized controlled trial (NCT06719024), which began on 29th November 2024 and is scheduled to end on 30th January 2026; it is ongoing and in the recruitment phase, with 20 patients expected to take part; it aims to investigate the efficacy and safety of topical ruxolitinib cream 1.5% in Chinese patients with non-segmental vitiligo on the face and neck, in whom previous treatment with topical tacrolimus was unsuccessful; the investigation is being carried out using ruxolitinib cream 1.5% and aqueous cream. [18] Lastly, an open-label, phase 2 study (NCT05750823) started on 11th April 2023 and is expected to end on 01st August 2025, involving the participation of 49 patients; it aims to assess the efficacy and safety of ruxolitinib cream in patients with non-segmental vitiligo with genital involvement; the intervention is being carried out with ruxolitinib cream. [19]

Safety

The safety of Ruxolitinib cream in patients with vitiligo was assessed in several clinical trials.

In the open label, phase II, proof-of-concept pilot trial (NCT02809976) (Table I), the most common adverse effects assumed to be related to the Ruxolitinib cream were rim of hyperpigmentation surrounding vitiligo lesion (9 patients, 81.82%), intermittent erythema over affected lesions (8 patients; 72.73%), URI symptoms (4 patients, 36.36%) and transient acne (2 patients, 18.18%). Other adverse events were gastroenteritis, dental pain, hypercholesterolemia, muscle aches, sore throat, traumatic blister and bee sting (all occurring in 1 patient, 9.09%). [2, 20]

In a phase II, randomized, double-blind, dose-ranging study (NCT03099304) (Table I), adverse effects were assessed over a period of 180 weeks, including 156 weeks of treatment and 6 months of follow-up. There was no increase in the risk of mortality for any of the doses used. As for the development of more serious adverse effects related to the treatment, the occurrence was rare and included coronary artery occlusion, subdural hematoma, achalasia, acute cholecystitis, osteoarthritis, breast cancer and seizures. With regard to less serious adverse effects, their occurrence was higher in the group of participants treated with 0.15% ruxolitinib cream once daily (61.29%). The most common dermatological side effects were contact dermatitis, application site pruritus, acne, application site erythema, as well as rash, skin exfoliation and urticaria. Most common adverse effects from other (non-dermatological) systems: bronchitis and nasopharyngitis. [2, 9, 10, 21]

In a phase II, interventional (NCT05247489) (Table I), adverse effects were evaluated over a period of approximately 52 weeks. There was no increase in the risk of mortality for both therapy options. Serious adverse effects only occurred in participants treated with topical ruxolitinib monotherapy, namely intestinal obstruction, perforation of the small intestine and generalized tonic-clonic seizures. Regarding less serious adverse effects, their occurrence was generally higher in the group of participants treated with topical ruxolitinib monotherapy, except for application site acne (11.43% in ruxolitinib cream combined with NB-UVB vs. 10% in ruxolitinib cream), oral herpes (8.57% vs. 0% respectively), upper respiratory tract infection (8.57% vs. 5%, respectively), procedural site reaction (11.43% vs. 0%, respectively) and skin hyperpigmentation (5.71% vs. 0%, respectively). In all cases, the most common adverse effects were application site acne (10.91%), upper respiratory tract infection (7.27%), procedural site reaction (7.27%), oral herpes (5.45%) and oropharyngeal pain (5.45%). Since the frequency of less serious adverse effects in lower in participants treated with ruxolitinib 1.5% cream BD and NB-UVB than in those treated with ruxolitinib 1.5% cream BD monotherapy (42.86% vs. 45%, respectively), the therapy combination seems to be well tolerated and beneficial for these patients. [22]

In two multinational, phase III, double-blind, randomized, vehicle-controlled clinical trials, TRuE-V1 (NCT04052425) (Table I) and TRuE-V2 (NCT04057573) (Table I), it was demonstrated that, given the low plasma ruxolitinib concentrations measured after the topical application of ruxolitinib cream, there were few treatment-related AEs other than those affecting the site of the application. During the 24-week double-blind phase of the trial, adverse events (AEs) were predominantly mild to moderate in severity. AEs were reported in approximately 50% of patients in the 1.5% ruxolitinib group and 33% of those in the vehicle group. Treatment-related application site AEs included acne, pruritus, and exfoliation. After 24 weeks, acne was the most frequently reported AE in both groups (5.8% in the ruxolitinib group vs. 1.2% in the vehicle group), followed by pruritus (5.1% vs. 2.6%). Systemic AEs, including nasopharyngitis, headache, urinary tract infection, and pyrexia, were also documented. However, their association with treatment was uncertain, as they occurred in fewer than 1% of subjects in the ruxolitinib group and were at least 1% less frequent than in the vehicle group. Furthermore, certain AEs were reported exclusively in either the ruxolitinib or vehicle group, with an incidence ranging from 0.5% to 1%. These included application site dermatitis, hypertension, anxiety, application site discoloration, application site folliculitis, contusion, contact dermatitis, diarrhea, ear infections, gastritis, gastroenteritis, hordeolum, influenza-like illness, insomnia, nasal congestion, and vomiting. No serious AEs were considered by investigators to be related to the trial medication. [1-4, 7, 9-11, 14, 15, 23, 24]

Ultimately, in a phase III, double-blind, vehicle-controlled, randomized withdrawal and treatment extension study (NCT04530344) (Table I), adverse effects were assessed up to approximately week 108 (week 52 was the first visit of this treatment extension study). Some serious AEs were reported, in 2.62% of patients receiving continuously 1.5% ruxolitinib cream BD, such as angina pectoris, otosclerosis, cholelithiasis, COVID-19 pneumonia, hip and spinal fracture, intervertebral disc disorder, spinal osteoarthritis, uterine leyomioma, bipolar I disorder, mental status changes, cystocele, pelvic prolapse, rectocele, uterine prolapse and acute failure. Other less serious AEs (such as COVID-19) occurred in 13% of patients treated with 1.5% ruxolitinib cream BD. [10, 25]

Combination therapy with ruxolitinib

Following the FDA's approval of topical ruxolitinib, possible therapeutic combinations that could be even more beneficial for the treatment of this disease have been investigated, particularly between topical ruxolitinib and NB-UBV: in a double-blind, randomized, dose-ranging phase 2 study of OPZ, the efficacy of combining OPZ and narrow-band ultraviolet B (NB-UVB) therapy observed during the open-label period at 52 weeks was confirmed at 104 weeks. [3, 5] F-VASI and T-VASI improved in 78.9% of patients and in 94.7% of patients, respectively, compared to the last assessment before the initiation of phototherapy, with mean improvement rates of 50.2% for F-VASI and 29.5% for T-VASI. [3, 5] Furthermore, among the 12 patients who did not achieve F-VASI 50 at week 24, improvements were observed in 83.3% of patients for F-VASI and in 91.7% of patients for T-VASI, with mean improvement rates of 47.8% and 31.1%, respectively. [3] In another study, 2 patients who had failed previous phototherapy and topical ruxolitinib monotherapy responded well in truncal lesions when treated with the combination simultaneously. [8] These findings suggest that the combination of ruxolitinib 1.5% topical application twice daily and NB-UVB therapy may be an effective treatment strategy for vitiligo, especially in ruxolitinib poor-responders. [3, 5, 7, 10]

The synergistic use of JAK inhibitors (JAKi), specifically topical ruxolitinib in this review, with phototherapy or natural sun exposure is supported by the hypothesis that repigmentation necessitates a dual approach: immune suppression by JAKi and melanocyte stimulation through low-dose phototherapy or sun exposure. [8, 9, 13]

Conclusions

Vitiligo is a common disease that disrupts daily activities and subsequently has an important impact on the quality of life of these patients.

The pathogenesis of this skin disorder is due to the progressive destruction and loss of melanocytes, primarily driven by autoreactive CD8+ cytotoxic T cells, leading to depigmented macules.

The JAK-STAT pathway regulates gene expression in response to various cytokines, playing a crucial role in immunity. In vitiligo, IFN-γ activates JAK1/JAK2 and STAT1/STAT2, driving inflammation and melanocyte destruction. JAKi block this signaling, reducing the inflammatory response. However, due to their variable specificity, JAKi can affect multiple immune pathways, requiring a balance between efficacy and safety.

Currently, vitiligo treatment essentially encompasses topical and systemic therapies, as well as phototherapy. With advancing knowledge of its pathogenesis, emerging therapeutic options are expected to become increasingly targeted and specific.

Ruxolitinib, a selective JAK1/2 inhibitor, disrupts vitiligo pathogenesis by blocking IFN-γ signaling, inhibiting dendritic cell migration and reducing cytotoxic T-cell activity, thereby facilitating melanocyte recruitment and repigmentation.

Based on phase II and IIII randomized controlled trials (namely, TRuE-V1 and 2), 1.5% ruxolitinib cream was approved in 2022, being the first topical JAKi approved to treat non-segmental vitiligo. Its twice-daily application to affected areas (BSA ≤10%) is indicated for patients aged ≥ 12 years with uncontrolled disease, since it has been shown to be effective and well tolerated. Additionally, the results showed improvements in F-VASI, T-VASI and BSA in several trials.

In general, Ruxolitinib led to the occurrence of some adverse effects, cutaneous manifestations being the most common, such as application site acne, pruritus, exfoliation and erythema. The frequency of reported upper respiratory tract infections also increased. These adverse effects rarely led to the discontinuation of the trial. No systemic accumulation of drugs has been reported, which may be beneficial in minimizing the systemic effects of other therapies.

Therefore, topical ruxolitinib has demonstrated efficacy and a favorable safety profile in patients with vitiligo, providing an additional therapeutic option, particularly for those who benefit from topical treatment over systemic therapy.

As mentioned above, some studies are still under development, particularly on the use of this topical drug in pediatric patients (under 12 years of age) and in cases of genital vitiligo.
In conclusion, ruxolitinib cream proved to be a very beneficial treatment for vitiligo.

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Appendix

Table I - IC_{50} and Ki values of Ruxolitinib in the in vitro enzyme assay system

JAK Inhibitors	IC_{50} or Ki (nM)				
		JAK1	JAK2	JAK3	TYK2
Ruxolitinib	**IC_{50}**	3.3	2.8	390	18
	Ki	1.3	0.36	7.0	1.6

Table II – Clinical trials on efficacy and safety of Topical Ruxolitinib

Study	Drug	Design	Outcomes	Results	Safety
NCT02809976 (Open Label Phase II Proof-of-concept Pilot Trial)[2, 20]	Ruxolitinib 1.5% Phosphate Cream	-11 participants (adults 18-65 years old) with: Vitiligo patches, BSA ≥ 1% -9 participants completed the trial - Ruxolitinib 1.5% phosphate cream applied BD for 20 weeks. No restriction on the area of application	Percent change in VASI at week 20 Percent change in BSA of repigmentation at week 20 Number of subjects achieving a PGVA of Clear or Almost Clear at week 20 Mean DLQI scores at week 20 Percent change in VEFT assessment – Disease Staging at week 20 Percent change in VEFT assessment – Disease Progression at week 20	Improvement in VASI on week 20 (mean): 23% BSA: 11.2% PGVA: 2 (18.2%) DLQI: 3 VETF – Disease staging: 4.5% VETF – Disease progression: -0.5%	<u>Treatment-emergent adverse effects:</u> Most common: rim of hyperpigmentation surrounding vitiligo lesion, intermittent erythema over affected lesions, URI symptoms and transient acne
NCT03099304 (Phase II, Randomized, Double-Blind, Dose-Ranging Study)[2, 9, 10, 21]	Ruxolitinib cream	-157 participants (adults 18-75 years old) with: Vitiligo and BSA <20% -randomly receiving one of four doses pf ruxolitinib cream (1.5% twice daily, 1.5% once daily, 0.5% once daily, 0.15% once daily) or vehicle (1:1:1:1:1) -Application for 52 weeks. No restriction on the area of application	F-VASI50, F-VASI75 and F-VASI90 at week 24 and 52 T-VASI50 at week 24 and 52 F-VASI and T-VASI improvement with a combined therapy (topical ruxolitinib and NB-UVB)	<u>Week 24 (1.5% ruxolitinib cream BD):</u> F-VASI50: 45% F-VASI75: 30% T-VASI50: 20% <u>Week 52 (1.5% ruxolitinib cream BD):</u> F-VASI50: 58% F-VASI75: 52% F-VASI90: 33% T-VASI50: 45% <u>104-week open-label extension period:</u> The additional NB-UVB (for 12 weeks) improved facial and total	Dermatological adverse effects: contact dermatitis, application site pruritus, acne, application site erythema, as well as rash, skin exfoliation and urticaria Most common adverse effects from other (non-dermatological) systems: bronchitis and nasopharyngitis

		-104-week open-label extension period (combination of topical ruxolitinib and NB-UVB)		body repigmentation	
NCT05247489 (Phase II interventional trial)[22]	Topical Ruxolitinib Phototherapy (NB-UVB)	-55 participants (adolescents and adults) with: non-segmental vitiligo and BSA <10%; 20 received ruxolitinib 1.5% cream BD (1) and 35 received ruxolitinib 1.5% cream BD combined with NB-UVB (2)	T-VASI25 at week 48 Percentage of participants achieving F-VASI50 at week 48 Percentage of participants achieving F-VASI75 at week 48 Percentage of participants achieving F-VASI90 at week 48 Percentage of participants achieving T-VASI50 at week 48 Percentage of participants achieving T-VASI75 at week 48 Percentage of participants achieving T-VASI90 at week 48 Percentage Change from baseline in F-BSA at week 48 Percentage Change from baseline in T-BSA at week 48	<u>Week 48 – (1):</u> T-VASI25: -3.43 <u>Week 48 – (2):</u> T-VASI25: -3.46 <u>Percentage of participants achieving F-VASI50 at week 48:</u> (1) 100% vs. (2) 96.2% <u>Percentage of participants achieving F-VASI75 at week 48:</u> (1) 100% vs. (2) 84.6% <u>Percentage of participants achieving F-VASI90 at week 48:</u> (1) 66.7% vs. (2) 53.8% <u>Percentage of participants achieving T-VASI50 at week 48:</u> (1)83.3% vs. (2) 57.7% <u>Percentage of participants achieving T-VASI75 at week 48:</u> (1)50% vs. (2) 19.2% <u>Percentage of participants achieving T-VASI90 at week 48:</u> (1)16.7% vs. (2) 7.7% <u>Percentage Change from</u>	Most common adverse effects: application site acne (10.91%), upper respiratory tract infection (7.27%), procedural site reaction (7.27%), oral herpes (5.45%) and oropharyngeal pain (5.45%) Less serious adverse effects were generally higher in the group of participants treated with topical ruxolitinib monotherapy

				baseline in F-BSA at week 48: (1)-78.06% vs. (2) -60.51% Percentage Change from baseline in T-BSA at week 48: (1) -47.03% vs. (2) -27.3%	
TRuE-V1 NCT04052425 (multinational, phase III, double-blind, randomized, vehicle-controlled clinical trial)[1-4, 7, 9-11, 14, 15, 23]	1.5% Ruxolitinib cream	-330 participants (adolescents and adults >12 years old) with: vitiligo and BSA ≤ 10% - Ruxolitinib 1.5% cream applied BD for 24 weeks and then for 28-week additional period. No restriction on the area of application -randomly (2:1) receiving 1.5% ruxolitinib cream (1) or vehicle (2) for 24 weeks - all patients received 1.5% ruxolitinib cream in the 28-week extension period (those who were previously receiving topical ruxolitinib continued with the same treatment (3) and those who previously received matching vehicle started being treated with ruxolitinib cream (4))	Percentage of participants achieving F-VASI25/50/75/90, T-VASI25/50/75/90, VNS of 4 or 5 at week 24 Percentage of participants achieving F-VASI25/50/75/90, T-VASI25/50/75/90 at week 52	Week 24 – percentage of participants achieving: F-VASI75: (1) 29.8% vs. (2) 7.4% F-VASI25: (1) 69.8% vs. (2) 30% F-VASI50: (1) 51.2% vs. (2) 16.9% F-VASI90: (1) 15.3% vs. (2) 2.2% T-VASI25: (1) 48.8% vs. (2) 23.8% T-VASI50: (1) 20.6% vs. (2) 5.1% T-VASI75: (1) 4.1% vs. (2) 1.8% T-VASI90: (1) 0.5% vs. (2) 0% VNS of 4 or 5: (1) 24.5% vs. (2) 3.3% Week 52 – percentage of participants achieving: F-VASI25: (3) 89.6% vs. (4) 74.4% F-VASI50: (3) 75.1% vs. (4) 56.1% F-VASI75: (3) 52.6% vs. (4) 26.8% F-VASI90: (3) 32.9% vs. (4) 12.2% T-VASI25: (3) 77.5% vs. (4) 56.1%	Treatment-related application site AEs: acne, pruritus, and exfoliation Systemic AEs: nasopharyngitis, headache, urinary tract infection, and pyrexia (their association with treatment was uncertain, due to their low frequency) Other AEs: application site dermatitis, hypertension, anxiety, application site discoloration, application site folliculitis, contusion, contact dermatitis, diarrhea, ear infections, gastritis, gastroenteritis, hordeolum, influenza-like illness, insomnia, nasal congestion, and vomiting No serious AEs were considered to be related to the trial medication

				T-VASI50: (3) 53.2% vs. (4) 31.7% T-VASI75: (3) 20.2% vs. (4) 9.8% T-VASI90: (3) 3.5% vs. (4) 2.4%	
TRuE-V2 NCT04057573 (multinational, phase III, double-blind, randomized, vehicle-controlled clinical trial)[1-4, 7, 9-11, 14, 15, 24]	1.5% Ruxolitinib cream	-344 participants (adolescents and adults >12 years old) with: vitiligo and BSA ≤ 10% - Ruxolitinib 1.5% cream applied BD for 24 weeks and then for 28-week additional period. No restriction on the area of application -randomly (2:1) receiving 1.5% ruxolitinib cream (1) or vehicle (2) for 24 weeks - all patients received 1.5% ruxolitinib cream in the 28-week extension period (those who were previously receiving topical ruxolitinib continued with the same treatment (3) and those who previously received matching vehicle started being treated with ruxolitinib cream (4))	Percentage of participants achieving F-VASI25/50/75/90, T-VASI25/50/75/90, VNS of 4 or 5 at week 24 Percentage of participants achieving F-VASI25/50/75/90, T-VASI25/50/75/90 at week 52	<u>Week 24 – percentage of participants achieving:</u> F-VASI75: (1) 30.9% vs. (2) 11.4% F-VASI25: (1) 63.9% vs. (2) 32% F-VASI50: (1) 51.4% vs. (2) 20.9% F-VASI90: (1) 16.3% vs. (2) 1.3% T-VASI25: (1) 50.2% vs. (2) 21.2% T-VASI50: (1) 23.9% vs. (2) 6.8% T-VASI75: (1) 8% vs. (2) 1.8% T-VASI90: (1) 1% vs. (2) 0% VNS of 4 or 5: (1) 20.5% vs. (2) 4.9% <u>Week 52 – percentage of participants achieving:</u> F-VASI25: (3) 82.5% vs. (4) 71.6% F-VASI50: (3) 74% vs. (4) 49.4% F-VASI75: (3) 48% vs. (4) 29.6% F-VASI90: (3) 27.7% vs. (4) 16% T-VASI25: (3) 76.8% vs. (4) 53.1% T-VASI50: (3) 49.2% vs. (4) 22.2% T-VASI75: (3) 20.9% vs. (4) 8.6% T-VASI90: (3) 6.8% vs. (4) 1.2%	*(AEs equal to those presented above for TRuE-V1)* <u>Treatment-related application site AEs:</u> acne, pruritus, and exfoliation <u>Systemic AEs:</u> nasopharyngitis, headache, urinary tract infection, and pyrexia (their association with treatment was uncertain, due to their low frequency) <u>Other AEs:</u> application site dermatitis, hypertension, anxiety, application site discoloration, application site folliculitis, contusion, contact dermatitis, diarrhea, ear infections, gastritis, gastroenteritis, hordeolum, influenza-like illness, insomnia, nasal congestion, and vomiting No serious AEs were considered to be related to the trial medication

NCT04530344 (phase III, double-blind, vehicle-controlled, randomized withdrawal and treatment extension study)[10, 25]	Topical Ruxolitinib	-458 participants (adolescents and adults aged >12years) with: vitiligo and BSA ≤ 10%	Percent change of F-VASI and T-VASI at week 104, in patients with no repigmentation or limited repigmentation of facial and non-facial lesions at week 24 of both TRuE-V1 and 2	<u>Week 104:</u> No previous repigmentation: improvement of F-VASI in 97.1% of patients and improvement of T-VASI in 93.3% of patients Previous limited repigmentation: improvement of F-VASI in 83.3% of patients and improvement of T-VASI in 81.6% patients Across both groups: 54.9% of patients achieved F-VASI and 50% achieved T-VASI50	Some serious AEs were reported in 2.62% of patients receiving continuously 1.5% ruxolitinib cream BD Other less serious AEs (such as COVID-19) occurred in 13% of patients treated with 1.5% ruxolitinib cream BD

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