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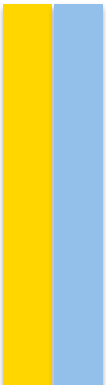
2022



The role of Tapinarof in the treatment of Psoriasis

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

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Junho de 2022

Assinatura do estudante:

Assinatura do orientador:

Agradecimentos
Ao Professor Doutor Tiago Torres, pela sua orientação ao longo deste trabalho e pela partilha de conhecimento.
Ao Simão Jacques Laranjeira Gomes, pela leitura atenta e correção linguística.

Resumo

A Psoríase é uma doença cutânea autoimune com incidência estimada a nível mundial de 1 a 3%. Caracteriza-se pela presença de placas eritematosas e descamativas na pele, ocorrendo períodos de remissão e de exacerbação da doença. Além disso, pode apresentar manifestações sistémicas associadas a múltiplas comorbilidades, que têm um impacto significativo na qualidade de vida.

Relativamente à etiologia, o aparecimento da doença pode ser devido a fatores genéticos, ambientais e imunológicos. No entanto, é claro que uma predisposição genética, associada a um *trigger* pode despoletar o início da doença. Para além disso, a fisiopatologia da Psoríase é multifactorial, marcada por níveis elevados de células T nas lesões de Psoríase que contribuem para a elevação de citocinas inflamatórias (IL-17 e TNFα).

Na última década, existiram grandes avanços no tratamento sistémico da Psoríase, essencialmente devido à descoberta dos fármacos biológicos. Existem tratamentos tópicos para doentes com apresentações mais leves da doença, os mais utilizados atualmente são os análogos da vitamina D e os corticóides. No entanto, existem limitações no uso destes fármacos, nomeadamente na duração do tratamento, nos locais de aplicação e nos efeitos adversos associados. Por isso, torna-se necessário a descoberta de novas opções de tratamento mais práticas e eficazes.

O recetor aril hidrocarboneto é um fator de transcrição que regula a expressão de genes em várias células. Em pele saudável, este recetor desempenha um papel importante na homeostase ao regular os mecanismos imunes, na diferenciação dos queratinócitos, na função de barreira da pele, e na resposta ao stress oxidativo. Atua ao nível da regulação da diferenciação de linfócitos TCD4+ em linfócitos Th17 e Th22 e consequente produção das citocinas pró-inflamatórias IL-17 e IL-22. Assim, surgiu o Tapinarof, que funciona como um modelador do recetor aril hidrocarboneto, fazendo o *downregulation* da interleucina 17, melhora a função de barreira da pele e tem propriedades antioxidantes.

Embora o mecanismo de ação e efeitos clínicos do Tapinarof ainda sejam desconhecidos, o mesmo tem vindo a ser divulgado como um novo tratamento para a Psoríase. Espera-se compilar o estado da arte do Tapinarof nesta revisão bibliográfica. Para isso foram utilizadas as bases de dados *PubMed* e *clinicaltrials.gov.* Resultando numa síntese do papel do Tapinarof como um novo fármaco tópico para o tratamento da Psoríase, incluindo, suas características farmacológicas e os resultados de ensaios clínicos publicados. Em suma, a partir deste trabalho espera-se avaliar a eficácia e segurança deste fármaco.

Palavras chave: Tapinarof, WBI-1001, GSK2894512, Psoriasis, Arly Hydrocarbon receptor

Abstract

Psoriasis is an autoimmune cutaneous disease with an estimated incidence of 1-3% worldwide. It is characterised by the presence of erythematous and scaly plaques in the skin. This disease presents with periods of remission and exacerbation. Additionally, it can also have systemic manifestations associated with multiple comorbidities, which significantly impact the quality of life.

Regarding its etiology, the onset of the disease can be due to genetic, environmental and immunological factors. However, it is clear that a genetic predisposition associated with a trigger can lead to the onset of the disease. Furthermore, the pathophysiology of Psoriasis is multifactorial, marked by high levels of T cells in psoriatic lesions, resulting in the elevation of inflammatory cytokines (IL-17 and TNFα).

In the last decade, there have been significant developments in the field of systemic treatments of Psoriasis, specially due to the discovery of biological drugs. Alternatively, there are topical treatments for patients with milder forms of the disease. The topical treatments that are most used today are vitamin D analogues and steroids. However, there are limitations in using these drugs; they can only be prescribed for a period of time, the sites they can be applied to and adverse effects. Therefore, it becomes necessary to discover new, more practical and effective treatment options.

The aryl hydrocarbon receptor (AhR) is a transcription factor that regulates gene expression in various cells. In healthy skin, this receptor plays an essential role in homeostasis by regulating immune mechanisms, keratinocyte differentiation, skin barrier function, and response to oxidative stress. Moreover, it plays a role in the regulation of the differentiation of CD4+ T lymphocytes into Th17 and Th22 lymphocytes and the consequent production of the pro-inflammatory cytokines IL-17 and IL-22. Thus Tapinarof was developed; it acts as a modulator of the aryl hydrocarbon receptor, downregulates interleukin 17, improves the skin's barrier function and has antioxidant properties.

Although Tapinarof mechanisms and its therapeutic outcomes are unknown, it has yet to be disseminated as a novel treatment for Psoriasis. It is hoped to correct this by compiling the state-of-art into a literature review. For this task, Pubmed databases and clinicaltrial.gov search engines were used to sample the state-of-the-art research in the field. Resulting in a synthesis of the role of Tapinarof as a new topical drug for the treatment of Psoriasis, including its pharmacological characteristics and the results of published clinical trials. In summation, from this work, it is hoped to judge the efficacy and safety of this drug.

Keywords: Tapinarof, WBI-1001, GSK2894512, Psoriasis, Arly Hydrocarbon receptor

List of abbreviations

C_{max} - maximum serum drug concentration
T_{max} - time for a drug to reach the maximum concentration
AhR- aryl hydrocarbon receptor
ARNT- aryl hydrocarbon receptor nuclear translocator
b.i.d- twice daily
BSA - Body Surface Area
CYP - cytochrome
EGFR- epidermal growth factors receptor
FLG - filaggrin
FLIM - fluorescence lifetime imaging microscopy
IL - interleukin
LOR - loricrin
MAPK - mitogen-activated protein kinases
NF-κB - nuclear factor-κB
NRF2 - nuclear factor erythroid 2-related factor 2
PASI - Psoriasis Area and Severity Index
PASI50 - ≥ 50% improvement in Psoriasis Area and Severity Index
PASI75 - ≥ 75% improvement in Psoriasis Area and Severity Index
PASI90 - ≥ 90% improvement in Psoriasis Area and Severity Index
PGA - Physician's Global Assessment
PK - pharmacokinetics
QD - once daily
ROS - reactive oxygen species
SD - standard deviation
STATs - signal transducer and activator of transcription
Th - T helper cell
TNFα - tumour necrosis factor alpha

Index

Table list

Figure List

Introduction

Psoriasis is a chronic inflammatory skin disease with an estimated incidence of 1-3% worldwide.[1-3] It affects both genders equally.[4, 5] Additionally, there are two mean onset age peaks for the disease, one between 16 and 22 years and the other between 57 and 60 years. In women, the disease tends to appear earlier.[6] Psoriasis is classified into different types of the disease, with plaque Psoriasis (or Vulgaris Psoriasis) being the most common.[4] Other phenotypes include guttate, pustular or erythrodermic.[4] Furthermore, it can be categorized according to the affected area, which includes inverse Psoriasis, sebopsoriasis, nail and palmoplantar Psoriasis.[4]

Chronic plaque-type Psoriasis is characterized by the presence of erythematous and scaly plaques in the skin, with periods of remission and exacerbation. [7, 8] The most prevailing areas of outbursts of lesions are the knees, the elbows and the sacrococcygeal region; also they can appear on the scalp and umbilical region. In the case of plaque-type Psoriasis, nail involvement is also frequent.[4] Systemic manifestations have also been reported, associated with multiple comorbidities, such as psoriatic arthritis, kidney disease, increased cardiovascular risk, and metabolic diseases, which can significantly impact the patient´s quality of life.[6, 9-11] Moreover, there is also a marked level of anxiety and depression in the patient population, associated with disfigurement and insecurity with their physical appearance. [8, 11]

Regarding etiology, genetic, environmental and immunological factors have been identified as responsible for the onset of the disease. A genetic predisposition associated with a trigger such as trauma, infection, stress, obesity, smoking or alcohol consumption can lead to the onset of the disease.[4] The pathophysiology of Psoriasis is multifactorial; it is known that there are high levels of T cells in psoriatic lesions that contribute to the elevation of inflammatory cytokines.[12] Specifically, the cytokines produced by Th17 cells, IL-17A, IL-17F and IL-22, lead to keratinization and secretion of more pro-inflammatory cytokines. [7, 13]

Significant progress has been made in systemic therapy of Psoriasis, essentially due to the discovery of biological drugs.[8] However, not all patients will benefit from systemic therapy, so it is essential to have topical treatment options, especially for milder forms of the disease.[8] Topical corticosteroids, vitamin D analogues, and coal tar are the most often prescribed topical therapies for mild Psoriasis.[2, 8] For the latter cases, there is a need to develop new non-steroidal topical Psoriasis therapies, as there are limitations in using these drugs, namely in the duration of treatment, application sites and associated adverse effects.[2, 8] As there is no cure for Psoriasis, these treatment aims to control the symptoms of the disease, enhancing the quality of life of the patients.[4]

A promising new drug called Tapinarof has been identified; it acts as a modulator of the aryl hydrocarbon receptor, which is a transcription factor that regulates gene expression in various cells.[11] It acts at the level of regulation of the differentiation of CD4+ T cells into Th17 and Th22 lymphocytes and the consequent production of the pro-inflammatory cytokines IL-17 and IL-22.[14] In fact, several novel research has demonstrated that Tapinarof improves skin's barrier function, has antioxidant properties and contributes to skin homeostasis.[15]

Objectives

This article aims to review the role of Tapinarof in the treatment of Plaque Psoriasis.

Methods

The state-of-art of the field was sampled using the Pubmed database and clinicaltrials.gov (up until December 2021) search engines. The key search terms employed consisted in combinations of the following medical terms: “Tapinarof”, “Psoriasis”, “WBI-1001”, “GSK2894512” and “Arly Hydrocarbon receptor”. The inclusion criteria took into consideration original or review articles written in English. An ad-hoc exclusion criteria was employed to the title and the abstract of 77 papers, resulting in a final of 50 articles as summarized in References.

Discussion

Pathogenesis of Plaque Psoriasis

Psoriasis is a chronic inflammatory immune-mediated disease.[9] Clinically, Plaque Psoriasis is characterized by limited erythematous scaly plaques in specific sites.[16] More commonly seen in extensor areas of knees, elbows, scalp, lumbosacral or umbilical area.[6] Histologically psoriatic lesions have epidermal hyperplasia (acanthosis) due to keratinocytes proliferation, infiltration of inflammatory cells and vasodilation.[3, 6, 16-18]

The etiology is multifactorial, including environmental and immune factors, but it also has a significant heritable component.[16, 17] It is believed that a trigger (infection, trauma, alcohol, smoke, drugs) allied to genetic susceptibility establish the onset of the disease, by activating an auto-inflammatory cascade.[17]

Psoriasis is distinguished by chronic inflammation, which results in uncontrolled proliferation and improper differentiation of keratinocytes and infiltration of T lymphocytes, dendritic cells and macrophages.[1, 19]

Its pathophysiology is mediated by cells from the adaptive and the innate immune system.[6, 19] One mechanism is marked by keratinocyte proliferation, induced by the migration of immune cells from the dermis to the epidermis.[15, 17] Here, the cells involved are Th1 and Th17 cells, which are considered to be related to Psoriasis pathogenesis by promoting the production of inflammatory cytokines, such as IL-17, IL-22, INF-γ and TNFα. These in turn lead to keratinocyte proliferation, which explains the high levels of pro-inflammatory cytokines present in psoriatic lesions.[3, 4, 12, 19] Another mechanism has Th22 cells, a subset of CD4+ T cells. They contribute to Psoriasis pathophysiology by inducing the production of IL-22 but do not interfere with IL-17 or INF-γ production.[17] These two mechanisms are not mutually exclusive as keratinocytes have been shown to also produce IL-32, which causes Th22 cells to produce TNFα, potentially activating pro-inflammatory Th22 responses.[7] Different types of Psoriasis are associated with distinct pathophysiology pathways; in Plaque Psoriasis, it is thought that TNF-α/IL-23/IL-17A pathway is the central axis, being a drug target in its biological treatment.[8, 19] However, the full picture is not yet, fully understood as skin microbiota have also been reported to play a role in Psoriasis by activating immune dysregulated responses.[19]

Current psoriasis treatment

Psoriasis is an incurable disease, but there are treatment options that aim to reduce the intensity of the symptoms, decrease disease activity and, therefore, improve the quality of life of the patients.[4]

The topical treatments most commonly given to Psoriasis are corticosteroids and vitamin D analogs, such as calcipotriene or calcitriol.[8] Besides these two, it is also possible to treat with vitamin A analogs (tazarotene), anthralin and coal tar.[8, 20] These medications have well-known adverse effects that limit their use in psoriatic patients, for example, skin irritation or inflammation associated with the use of vitamin A analogs.[8] In terms of topical corticosteroids, the main problem remains with the exacerbation of the disease symptoms between cycles of corticoid prescription.[8] In addition, steroids have limitations regarding the skin areas where they can be employed.[21]

In terms of topical options, it is also relevant to consider the patient's preferences to ensure therapeutic adherence, as some patients prefer creams over ointments, arguing it is easier to apply.[21]

Besides topical therapy, depending on the severity of the disease, systemic therapies can be prescribed, including retinoids, methotrexate, cyclosporine and biologics; the latter act on the disease by blocking the activity of Th cells and the production of cytokines, such as TNFα, IL-17, IL-23.[9] In addition, phototherapy is also a treatment option, which has been shown to induce local immunosuppression.[4]

In recent years, new systemic treatments for Psoriasis have been discovered, especially suitable for patients with high severity of the disease.[22] Additionally, patients with restricted skin involvement may not benefit from systemic treatment. Therefore, new topical drugs for Psoriasis must be developed.[22] Despite the significance of topical medicines in Psoriasis and the increased demand for more effective and well-tolerated topical therapies, few novel therapies have made it to market in recent years. [8]

To score the efficacy of novel Psoriasis treatments, scales have been created; here three are discussed. The first is the Psoriasis Area and Severity Index (PASI) score, which runs from 0 to 72 and assesses Psoriasis severity and extent. A higher PASI score implies that the condition is more serious.[23] The second is the physician global assessment (PGA) score, which evaluates erythema, induration and scaling in psoriatic lesions; it goes from 0 (healthy skin) to 5 (very severe).[23] The final one is the Body Surface Area (BSA), which estimates the percentage of the body covered by Psoriasis. This score ranges from 0% to 100%.[23]

The role of aryl hydrocarbon receptor

Arly hydrocarbon receptor (AhR) is a cytosolic ligand-dependent transcription factor expressed in different types of skin cells (keratinocytes, fibroblasts, mastocytes, and melanocytes).[11, 18, 24, 25] In the epidermis, it is more commonly seen in the granular and spinous layers, and it is primarily generated in the liver, lung, gut, and skin. [1, 26] In healthy skin, AhR signalling is essential for

maintaining skin homeostasis through regulating the skin immunological network, keratinocyte differentiation, skin barrier function, and gene expression in cells.[27, 28]

This receptor can bind to endogenous or exogenous agents such as pollutants, polycyclic aromatic hydrocarbons (PAHs), microbial products, dietary ligands, and phytochemicals that activate the AhR.[1, 8, 12, 24, 29, 30] FICZ (6-formylindolo[3,2-b]carbazole) is a high affinity AhR agonist and tryptophan derivative, generated after UVB light exposure.[24, 31, 32] TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) is an exogenous AhR ligand and is classified as a pollutant.[33] A study concluded that TCDD binding to AhR leads to the development of Psoriasis by increasing the expression of AhR regulatory genes, such as CYP1A1, IL-17, and IL-22.[33]

Arly hydrocarbon receptor is located in the cytosol in association with chaperones that play several tasks such as maintaining the stability, ensuring its functionality, and avoiding its destruction.[25] When a ligand binds to the receptor, the AhR-ligand complex migrates to the nucleus and dimerizes by the AhR nuclear translocator (ARNT).[8, 25, 34, 35] The AhR-ligand-ARNT complex attaches to specific DNA recognition sites, causing the transcription of genes.[8, 25, 26] Furthermore, cytochrome P450 enzymes (CYP1A1, CYP1A2, and CYP1B1) can be transcripted by this mechanism and then metabolize AHR ligands.[36]

Thus, the differential activation of AhR by such a diverse set of ligands, depending on the cell in which it is taking place, can activate or suppress various genes, resulting in various physiological responses.[8]

Arly hydrocarbon receptor and Psoriasis

It has been hypothesised that AhR plays a role in the pathogenesis of inflammatory skin diseases.[28] Researchers defend that there are two AhR signalling pathways.[37] The canonical activation pathway (AHR: ARNT signalling), which induces carcinogenesis, hyperpigmentation and disables apoptosis[37] and conversely, the non-canonical AhR signalling activation (includes other pathways such as EGFR, MAPK, NF-κB, STATs, NRF-2), which induces inflammation, abnormal barrier function, hypopigmentation, production of cytokines and oxygen reactive species.[37]

This pathway has been recognised as a potential therapeutic target, with topical crude coal tar being believed that because it is made by polycyclic aryl hydrocarbons, it can activate AhR.[38]

Moreover, in psoriatic skin, the aryl hydrocarbon receptor is present in the cutaneous lesions and regulates the inflammatory response as well as the terminal differentiation of keratinocytes and T lymphocytes.[1, 8] In Psoriasis, there is impairment of genes that take a role in the catabolism of tryptophan products, and consequently, there will be a decrease of FICZ, leading to less activation of AhR and higher expression of inflammatory cytokines.[24]

When comparing psoriatic patients to healthy individuals, the former presented increased serum levels of AhR.[1] In addition, it was concluded that there was greater AhR expression, related to increased levels of Th22 cells and IL-22, distinct from healthy individuals.[39] This hypothesis is further corroborated by the work of Kim, H.O et al., that applied two pollutants that act as AhR ligands to keratinocytes from healthy participants, and it was observed that the production of inflammatory cytokines increased[40] Similarly, another study analyzed the activated peripheral blood mononuclear cells of psoriatic patients and found that they presented higher AhR-regulated factors, such as IL-22 and IL-17, compared to healthy participants.[33]

A study conducted by Di Meglio et al. investigated the effects of AhR activation and inhibition in vitro, with human psoriatic skin samples, and in vivo, with a mouse animal model of psoriasiform skin inflammation. It was shown that this receptor deficit causes increased responsiveness to pro-inflammatory stimuli and the development of uncontrolled inflammation in psoriatic skin. AhR-deficient mice experienced marked psoriasiform skin inflammation with elevated IL-17 and IL-22 production in an imiquimod-induced Psoriasis model compared to controls. Both models also presented increased inflammatory cytokines when antagonism of AhR was administrated and, conversely, decreased when agonism was administrated. In addition, it was demonstrated that in the deficient mouse skin models, dysregulation of keratinocytes and fibroblasts was observed. However, it has been demonstrated that IL17 cytokine is not the only intervenient in the development of psoriasiform inflammation, as inflammation was not attenuated in AhR-deficient mice when IL17 was blocked. [30]

Synthet AhR ligands have also been investigated, with the work by Cardinali et al. identifying NPD-0614-13 and NPD-0614-24, which are structurally similar to FICZ, as candidates. A model of skin Psoriasis that is able to simulate the epidermis thickness, the presence of fibroblasts and the activity of pro-inflammatory cytokines showed that these ligands reduced the production of pro-oxidative cytokines and reduced the amount of intracellular reactive oxygen species. Therefore, they might be safe AhR ligands and potential efficacious treatments of Psoriasis.[24]

An additional therapeutic target has been identified by JE Kim et al. The latter´s work showed that the higher expression of AhR was correlated with an increased expression of CYP1A1 ($p < 0.001$ for both) in psoriatic compared to healthy skin; however, the size samples were small (24 patients with Psoriasis and 10 controls).[41] However, although expression of CYP1A1 is associated with increased activation of AhR in keratinocytes, no statistical significance was found regarding Psoriasis severity.[1]

In conclusion, there is ever growing evidence that AhR plays a vital role beyond the one accepted in skin homeostasis and integrity, as a potential therapeutic target in inflammatory diseases.[37]

The kind of AhR ligand and the cell environment are crucial elements that can influence AhR-driven signals differentially, functioning as inhibitors or stimulators of inflammatory processes.[24] Hence, further investigation to elucidate what is the role of AhR in Psoriasis is needed.[25, 37]

Tapinarof

A potential drug was found in Tapinarof (previously named WBI-1001 or GSK2894512 cream), which is a topical aryl hydrocarbon receptor modulator with a natural origin.[8] Its effects were observed from the interactions of the nematode of the genus *Heterorhabditis* with insects. The nematode carries inside his gut a gram-negative bacteria with luminescence properties called *Photorhabdus luminescens,* and it was shown that when the nematode infects an insect, *P.luminescens* is released and kills the insect host by producing metabolites.[8, 42, 43] It was discovered that insects infected by the nematode did not putrefy after death, in contrast to the fast degradation observed in the absence of the parasite.[8, 42, 44] As a result, it was hypothesized that *P. luminescens* produced metabolites with antibacterial qualities responsible for the observed biologic action.[8, 43] One such metabolite, 3,5-dihydroxy-4-isopropylstilbene (Tapinarof), was isolated and identified.[8, 45]

Tapinarof was discovered to bind directly to AhR, resulting in the suppression of inflammatory cytokines, the modulation of skin barrier protein expression, and antioxidant activity.[8, 14]

Benvitimod is a drug with the same active principle but a different vehicle; consequently, it has a similar mechanism of action as Tapinarof.[46] WBI-1001 is a prior formulation that was then modified to improve the drug's stability and distribution.[8]

Pharmacodynamics and Pharmacokinetics

The chemical formula of Tapinarof is 3,5-Dihydroxy-4-isopropylstilbene (also known as 5-[(E)-2-phenylethenyl]-2-[propan-2-yl]benzene-1,3-diol).[14, 47] Its molecular weight is 254 g/mol.[8]

Tapinarof targets the aryl hydrocarbon receptor and acts as an agonist of AhR.[34] It activates the nuclear factor erythroid 2-related factor 2 (NRF-2) pathway and consequently produces antioxidative enzymes that limit oxidative stress (Figure 1).[8, 11, 27] Tapinarof induces the production of loricrin (LOR) and filaggrin (FLG), by activating transcription factor OVO-like 1 (OVOL1); these proteins play an important role in maintaining skin barrier function (Figure 1).[27, 34]

In terms of immunological function, AhR activation by Tapinarof regulates the differentiation of T-helper (TH17) and T regulatory cells, leading to the downregulation of IL17 (Figure 1) and consequently will reduce inflammation in psoriatic skin.[27]

Some authors defend that the mechanism of action of Tapinarof does not only depend on the activation of AhR but also on the microbiome of the skin. There are high levels of pro-

inflammatory cytokines in psoriatic skin, possibly due to abnormal immune reactions to the skin microbiome. Tapinarof can lead to the destruction of microorganisms present in psoriatic skin by attenuating cytokine production and, consequently, improving the disease.[48]

A phase I study evaluated the PK of Tapinarof cream 1% and 2% applied twice daily in 11 participants with atopic dermatitis. Five patients received Tapinarof cream 1%, and six received Tapinarof cream 2%; the plasma concentration was evaluated on days 1 and 21. Three patients from the 2% arm discontinued the trial because of adverse effects. It was shown that a higher concentration of Tapinarof cream leads to greater plasma concentrations of the drug, which tend to decrease over time which proves that there is no accumulation after the repeated exposure. On day 1, the mean maximum serum concentration (C_{max}) for Tapinarof 2% and 1% was 2.5 ng/mL and 1.2 ng/mL, respectively. At day 21 it was 0.3 ng/mL for the 2% cohort and 0.15 ng/mL for the 1% cohort. The value of the median time to reach the maximum serum concentration (T_{max}) for both concentrations of tapinarof cream was between 1 and 4 hours.[14]

Regarding the pharmacokinetic profile of Tapinarof 1% applied once daily, it was observed that the mean concentration was 898 pg/mL on day 1, decreasing overtime measuring a mean concentration of 116 pg/mL on day 29. It was considered that this might be because the skin's barrier function was restored. The plasma concentration of Tapinarof 1% cream hits T_{max} in a mean of 4,49h, within a range of 2 to 5h post administration of the first dose.[5]

Additionally, biodistribution and residency of GSK2894512 were evaluated in a phase I trial that included six healthy volunteers and used fluorescence lifetime imaging microscopy (FLIM), a non-invasive method limiting the use of skin biopsies. It was taken using GSK2894512 luminous properties; the cream was applied for seven days, and images were taken every day before the drug administration. It was shown that in the first days, the cream remained in the superficial layers of the skin, at day ten, there was no fluorescence detected.[49]

Tapinarof metabolism is hepatic, with cytochrome (CYP) P450 playing a determinant role. The primary enzymes involved are CYP1A2 and CYP3A4. Conversely, CYP2C9, CYP2C19, CYP2C20, CYP2D6 play minimal roles in the oxidative metabolism of Tapinarof in hepatocytes.[14] Due to the large number of CPY enzymes involved in tapinarof metabolization, inhibiting one of them would not necessarily, result in increased tapinarof exposure.[14]

Efficacy

The efficacy of Tapinarof in patients with mild to moderate Plaque Psoriasis was assessed in several clinical trials, as presented below.

Starting with a phase IIa, multicenter, open-label trial (NCT04042103) (Table I) that assessed the efficacy of Tapinarof in treating patients with extensive Plaque Psoriasis. The study population

included 21 adult patients, but only 19 completed the trial. The reasons for discontinuation were due to lost of follow up in one patient, and another withdrew from the study. Tapinarof cream 1% was applied once daily for 29 days to all the affected areas. The efficacy was evaluated by comparing the Patient Global Assessment (PGA), Psoriasis Area and Severity Index (PASI) and the percentage of Body Surface Area (BSA) on day 1 and day 29. At baseline, twelve patients had a PGA of 3 and seven patients a PGA of 4. On day 29, fourteen patients (73,7%) had a ≥ 1 grade PGA improvement, and six patients had a ≥ 2 grade improvement compared to day 1. Four patients (21,1%) achieved a PGA score of 0 or 1 and ≥ 2 grade improvement in PGA. At baseline, the mean of PASI was 24,65 (SD: 7,146). On day 29, there was a significant mean change in PASI score to 15,14 (95% CI – 19,61 to – 10,66). Eighteen patients improved their PASI score during this trial. Seven patients achieved PASI75. On day 1, the mean percentage BSA was 27,20 (SD: 7,481). On day 29, there was a change in the mean percentage BSA to 14,44 (95% CI – 19,84 to – 9,04). So this demonstrates that patients reached milder forms of the disease with this treatment.[5]

Two recent phase III trials have been conducted to explore the efficacy and safety of Tapinarof as a new topical option for the treatment of Plaque Psoriasis. PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980) were two multicentre, randomized, double blind, vehicle controlled trials that included participants aged between 18 and 75 years old with mild-to-severe plaque Psoriasis with stable disease for at least six months and BSA between 3% to 20% and a PGA score of at least of 2. PSOARING 1 (Table I) study had 510 participants, and PSOARING 2 (Table I) had 515 participants. The subjects were randomized in a 2:1 ratio, receiving vehicle cream or 1% Tapinarof cream once daily for 12 weeks. The primary outcome was PGA response, considered a PGA score of 0 or 1 and at least 2-grade improvement from baseline at week 12. In both studies, a significantly higher proportion of patients in the tapinarof arm met the primary endpoint than vehicle cream at week 12. In PSOARING 1, the proportion of subjects achieving PGA response was 35,4% in the tapinarof 1% cream arm ($p < 0.001$ vs vehicle) and 6,0% for vehicle cream. In PSOARING 2, the percentage of subjects achieving the primary endpoint was 40,2% for Tapinarof 1% cream ($p < 0.001$ vs vehicle) and 6,3% for vehicle cream. Overall, in the two studies, at week 12, PASI 75, PGA score of 0 or 1, BSA changes and PASI 90 were observed in a significantly higher proportion of patients in the Tapinarof 1% cream arm.[50]

A phase II, doubleblind, randomized, vehicle controlled study (NCT02564042) (Table I) in which 227 participants aged 18 to 65 were randomly assigned in a 1:1:1:1:1:1 ratio, receiving once or twice daily vehicle cream or Tapinarof cream 0.5% or 1% for 12 weeks and follow up of 4 weeks after the end of study treatment. Each arm had 38 patients. For this study, the primary outcome was PGA response, which included the proportion of patients achieving at week 12 PGA score of 0 or 1 and at least an improvement of 2 points comparing to baseline. At week 12, it was shown to

be statistically significant that it was more frequent to achieve a PGA score of 0 or 1 and PASI 75 in the Tapinarof groups than the vehicle treatment groups. This response started at week 2 of treatment, and it was maintained during four weeks of follow-up.[22] Additional outcomes were evaluated in a phase IIb (Table I) study, which consisted of patients achieving PASI 50, PASI 75 and PASI 90, mean changes in PGA score and total target lesion grading score. At week 12, the percentage of patients who achieved PASI 50 was between 71% to 92% in the Tapinarof group compared to 10% to 32% in the vehicle group (all $p < 0.001$). PASI 75 was reached at week 12 in 65% ($p = .001$) and 56% ($p<.001$) of participants in the Tapinarof 1% group, twice or once daily, respectively. In the 0,5% Tapinarof group PASI 75 was achieved in 46% in both twice or once daily applications ($p = .035$, and $p = .002$, respectively). In the control group, 16 % (twice daily) and 5% (once daily) reached PASI 75. For PASI 90 39% ($p=.002$) and 40% ($p = .001$) of participants in the 1% Tapinarof group, and 31% ($P = .008$) and 18% ($P = .057$) of participants in the 0,5% Tapinarof group, twice or once daily respectively. In the vehicle group, 0% of participants reached PASI 90 at week 12. In addition, it was also consider as a measure of efficacy the changes in the mean PGA from baseline and the PGA response rate, which was more efficacious in all Tapinarof groups and maintained for four weeks after the end of the study. Lastly, in evaluating the total target lesion grading scores from baseline, there was a higher reduction in the Tapinarof groups than the vehicle, beginning at week two and maintained until week sixteen.[21]

WBI-1001 has also been investigated and proved to be effective in treating Psoriasis.

Bissonnette et al. carried out a phase IIa randomized, double-blind, placebo-controlled research (Table I) to assess the safety and effectiveness of topical WBI-1001 1% in a cream formulation for the treatment of Psoriasis. This study included 61 female and male volunteers aged between 18 and 65 diagnosed for at least six months with stable, mild to moderate plaque Psoriasis. Patients are required to have Psoriasis on between 1% and 10% of their BSA (excluding the face, groin, scalp, and genital areas) and a PGA of two (mild) to four (severe) at Day 0. They were randomly assigned (2:1) to receive either 1.0% WBI-1001 cream or a placebo cream twice daily for 12 weeks. The following outcomes were used in this study: the change from baseline in PGA at Day 84, the proportion of patients who attained a PGA of 0 or 1 at Day 84, PASI 50 and PASI 75 at Day 84. On Day 84, there was a statistically significant difference in PGA change from baseline between placebo and WBI-1001. Individuals assigned to WBI-1001 had a 67.5% chance of achieving a PGA of 0 (clear) or 1 (almost clear) at Day 84, compared to 4.8% for patients randomized to placebo ($P < 0.0001$). At week 12, BSA was reduced by 79.1% in patients assigned to WBI-1001, whereas it increased by 9.4% in participants randomized to placebo ($P < 0.0001$).[2]

Safety

The safety of Tapinarof in patients with mild-moderate Plaque Psoriasis was assessed in several clinical trials.

In the phase IIa trial (NCT04042103) (Table I), the most common adverse effects assumed to be related to the Tapinarof cream were folliculitis (four patients, 19%) and headache (4 patients, 19%). Other adverse effects were back pain and pruritus. This drug was well tolerated even in sensitive areas. There were no cardiac side effects reported, such as prolongation of QT interval.[5]

In the PSOARING 1 and PSOARING 2 phase III trials (Table I), adverse effects were more common in the Tapinarof group, with 50,3% and 54,5% of the patients, respectively. The most common adverse effects reported were: folliculitis, contact dermatitis, headache and pruritus. In the first trial, one episode of severe folliculitis was reported, and 1,8% of patients in the Tapinarof arm discontinued the trial. In the two trials, one severe adverse event of contact dermatitis was reported and led to the discontinuation in 1,5% and 2,0% of patients in trials 1 and 2, respectively. A scale was applied to evaluate burning, stinging, and itching, and it was rated as low in both trials.[50]

In a phase II trial (NCT02564042) (Table I), the treatment-emergent adverse effects were more common in the tapinarof groups, but they were tolerable with mild to moderate severity. The most frequent were folliculitis (9%) and contact dermatitis (3%). Some patients discontinued this trial due to adverse effects, being also more common in the tapinarof groups, mainly due to contact dermatitis and application site dermatitis. There were no reports of cardiac or laboratory alterations.[22] A phase IIb multicentre, double-blinded, a vehicle-controlled trial conducted by Stein Gold L et al. (Table I), where participants were randomized in a 1:1:1:1:1:1 ratio, receiving once or twice daily vehicle cream or tapinarof cream 0.5% or 1% for 12 weeks evaluated the safety of tapinarof treatment. The adverse effects that were reported had mild to moderate severity. It was applied tolerability scores considering the participants and the investigator's point of view for 12 weeks. Participants scored 0 to 1, which means none or slightly site burning and itching on the application site. The investigators scored mostly 0.[21]

The safety profile of the phase II study conducted by Bissonnette et al. (Table I) was in line with the previous studies on Tapinarof as a new treatment for Psoriasis. The most common treatment-emergent adverse events were hyperpigmentation, dermatitis, folliculitis, and papules with mild to moderate intensity. Three patients discontinued the trial, two from the WBI-1001 arm because of dermatitis and another from the placebo group due to a cerebrovascular accident not considered related to the study drug.[2]

Conclusions

Psoriasis is a common disease that disrupts daily activities and consequently has a significant impact on the quality of life of these patients.

The pathogenesis of Psoriasis is due to uncontrolled proliferation and abnormal differentiation of keratinocytes leading to acanthosis, infiltration of inflammatory cells and vasodilation.

Arly hydrocarbon receptor is a cytosolic ligand expressed in several skin cell types. AhR expression in the epidermis can be triggered by endogenous and exogenous agents, leading to different responses. AhR signalling is required in healthy skin to maintain skin homeostasis by regulating the skin immunological network, keratinocyte differentiation, skin barrier function, and gene expression in cells. In psoriatic skin, it is believed there is a higher expression of AhR, although it is needed further studies to clarify its role in Psoriasis.

There is currently a wide variety of options for the treatment of Psoriasis, and, with the advancement of knowledge about its pathogenesis, new treatment options will become increasingly specific. Currently, Plaque Psoriasis treatment is divided into topical, systemic therapy and phototherapy. There is a need for more topic therapeutic options, especially for mild to moderate disease.

Tapinarof addresses the obstacles of the existing topical therapeutics by acting as an AhR agonist. Its mechanism of action has three main effects: production of skin barrier proteins, downregulation of IL17 and reduction of reactive oxygen species, therefore reducing inflammation.

Tapinarof has shown to be effective and well tolerated in phase II and phase III randomized controlled trials in patients with mild to moderate severity Plaque Psoriasis. Most trials evaluated tapinarof cream 1% applied once daily, which could be an excellent choice to guarantee therapeutic adherence and treatment success. In addition, the results showed improvement in PASI, PGA and BSA in most trials.

In general, Tapinarof led to the development of some adverse effects, being cutaneous manifestations the most common. Pruritus, folliculitis, contact dermatitis and headache were frequently reported as adverse effects. Although, the intensity of these symptoms was mild to moderate with spontaneous resolution and rarely led to the discontinuation of the trial. It is not known the reason for the development of headaches. No systemic drug accumulation has been reported, which can be beneficial for these patients because of the need to use topicals for long periods is expected. Increased risk of severe adverse effects, such as cardiac side effects and prolongation of QT interval, was not seen in any clinical trials.

Therefore, Tapinarof has shown to be effective and has a favourable safety profile in the psoriatic patients, representing one more treatment option for this population, particularly those who benefit from being treated with topical therapy over systemic.

Further research is needed to determine this medication's long-term efficacy and safety in Plaque Psoriasis. In addition, it would be interesting to compare it to other topical therapies for Psoriasis. A phase III study (NCT04053387) is in underway to assess the effectiveness and safety of Tapinarof in adults over forty weeks of therapy and four weeks of follow-up. There is also a phase III trial targeted at the pediatric population with Plaque Psoriasis; it is yet in the recruiting status.

To conclude, Tapinarof is a small molecule of bacterial origin that has the potential to become a non-steroidal topical treatment for plaque Psoriasis. It is hoped that the approval of the Tapinarof will come soon.

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Appendix

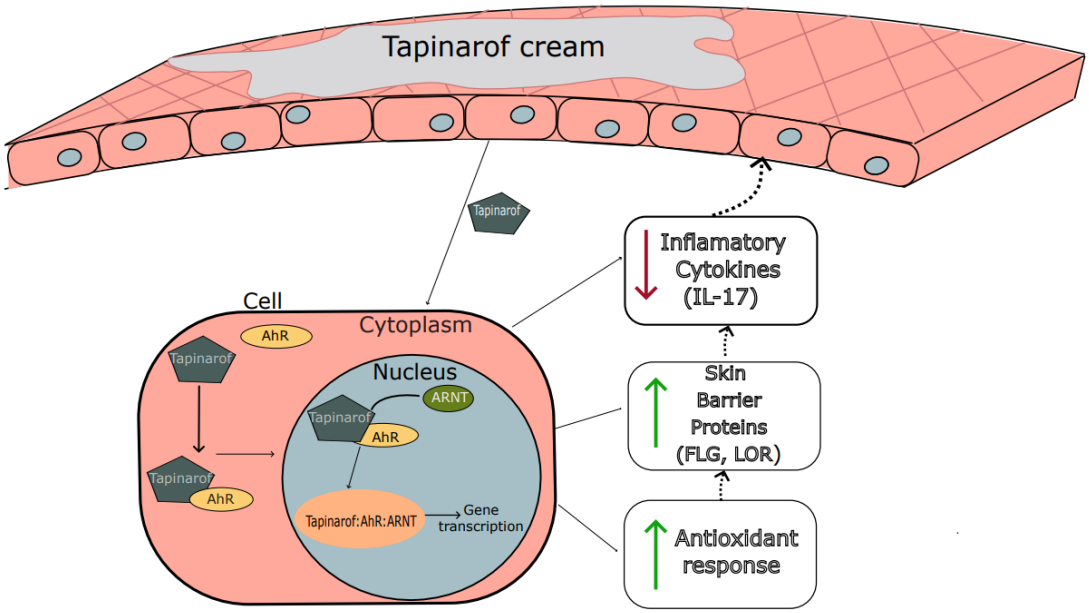

Figure 1 – Tapinarof mechanism of action

Table I - clinical trials on efficacy and safety of Tapinarof and WBI-1001

Study	Drug	Design	Outcomes	Results	Safety
NCT04042103[5] (Phase IIa, multicenter, open-label trial)	Tapinarof	- 21 participants (adults) with: -Plaque Psoriasis -PGA ≥ 3 -BSA ≥20% - 19 participants completed the trial - Tapinarof cream 1% applied QD for 29 days. No restriction on the area of application.	**Primary** Evaluate the safety, tolerability, efficacy (PGA, PASI and BSA) and PK of tapinarof cream 1% QD **Secondary** Exclude clinically relevant effects of tapinarof cream 1% QD on the QT interval	**Improvement in PGA score on day 29:** ≥ 1-grade: 14 patients (73.7%) ≥ 2-grade: 6 patients (31.6%) PGA 0 or 1 and ≥ 2-grade: 4 patients (21.1%) **PASI:** Mean day 1: 24,65 Mean day 29: 15,14 PASI75: 7 patients (36,8%) **% BSA:** Mean day 1: 27,20 Mean day 29: 14,44	Treatment-emergent adverse effects Folliculitis (19%) Headache (19.0%) Others: Back pain Pruritus Contact dermatitis
PSOARING 1[50] NCT03956355 (Phase III, multicentre, randomized, double blind, vehicle controlled trial)	Tapinarof	-510 patients aged 18-75 with: - mild to severe Plaque Psoriasis -BSA ≥3% - ≤20% -PGA ≥ 2 2 arms (2:1, 12 weeks): -1% Tapinarof cream QD (n=340) -Vehicle cream QD (n=170)	**Primary** PGA response: PGA score of 0 or 1 and a decrease of ≥ 2-5 points at week 12 **Secondary** Changes in the baseline of BSA, PGA score of 0 or 1, PASI 75 and PASI 90 at week 12.	**Primary:** 35,4% - Tapinarof arm (p<0,001 vs vehicle) 6% - Vehicle arm **Secondary:** **PASI 75** 36,1% - Tapinarof arm (p<0,001 vs vehicle) 10,2% - Vehicle arm **PGA score of 0 or 1** 37,8% Tapinarof arm 9,9% - Vehicle arm (p<0,001 vs vehicle) **BSA changes** -3,5% - Tapinarof arm (p<0,001 vs vehicle) -0,2% - Vehicle arm **PASI 90** 18,8% - Tapinarof arm (p<0,001 vs vehicle) 1,6% - Vehicle arm	Treatment-emergent adverse effects Tapinarof arm: 50,3% Vehicle arm: 22,4% Most common: folliculitis, contact dermatitis, headache, pruritus
PSOARING 2[50] NCT03983980 (Phase III, multicentre, randomized, double blind, vehicle controlled trial)	Tapinarof	515 patients aged 18-75 with: -Plaque Psoriasis - BSA ≥3% - ≤20% - PGA score ≥ 2 2 arms (2:1, 12 weeks): -1% Tapinarof cream QD (n=343) -Vehicle cream QD (n=172)	**Primary** PGA response: PGA score of 0 or 1 and a decrease of ≥ 2-5 points at week 12 **Secondary** Changes in the baseline of BSA, PGA score of 0 or 1, PASI 75 and PASI 90 at week 12.	**Primary:** 40,2%- Tapinarof arm (p<0,001 vs vehicle) 6,3% - Vehicle arm **Secondary:** **PASI 75** 47,6% - Tapinarof arm (p<0,001 vs vehicle) 6,9% - Vehicle arm **PGA score of 0 or 1** 43,6% - Tapinarof arm (p<0,001 vs vehicle) 8,1% - Vehicle arm **BSA changes** -4,2% - Tapinarof arm (p<0,001 vs vehicle) -0,1% - Vehicle arm	Treatment-emergent adverse effects Tapinarof arm: 54,5% Vehicle arm: 26,2% Most common: folliculitis, contact dermatitis, headache, pruritus

				PASI 90 20,9% - Tapinarof arm (p<0,001 vs vehicle) 2,5% - Vehicle arm	
Stein Gold L et al. (Multicenter, phase 2b, double blinded, randomized, vehicle-controlled study)[21]	Tapinarof	227 patients aged 18-65 with: -Plaque Psoriasis -BSA ≥1% - ≤15% -PGA ≥2 Randomized 1:1:1:1:1:1 receive during 12 weeks: -Tapinarof cream 0.5% or 1% QD or b.i.d -vehicle cream QD or b.i.d 4 weeks of follow up	**Efficacy outcomes:** PGA response Change in mean PGA Total target lesion grading scores % patients achieving PASI50, PASI75, and PASI90.	**PGA response:** Higher in all tapinarof cream groups compared with vehicle group **Mean improvements in PGA scores** from baseline: Higher in all tapinarof groups compared to vehicle. **Total target lesion grading** Higher reductions in in all tapinarof groups beginning at week 2. (P <0.001) **PASI50, PASI75, PASI90** Higher responses starting at week 2 compared to vehicle cream, and superior efficacy maintained until week 12 and 4 weeks after the treatment.	Treatment-emergent adverse effects Mild to moderate in severity Tolerability scores: Patient: Score of 0 or 1 - none or slight application site burning/stinging and itching during 12 weeks Investigator: Predominantly 0 (no irritation) through 12 weeks No skin atrophy.
Robbins et al (Phase 2, randomized, double-blind, vehicle-controlled study-NCT02564042)[22]	Tapinarof	227 patients aged 18-65 with: -Stable Plaque Psoriasis (≥ 6 months) -BSA ≥1% - ≤15% -PGA score ≥ 2 Randomized in 6 arms (1:1:1:1:1:1, 12 weeks): 1% tapinarof b.i.d (n=38) 1% tapinarof QD (n=38) 0.5% tapinarof b.i.d (n=38) 0.5% tapinarof QD (n=38) Vehicle b.i.d (n=38) Vehicle QD (n=38) 175 patients completed the trial	**Primary** % of patients with a PGA score of 0 or 1 at week 12 ≥2-grade improvement in PGA score from baseline **Secondary:** % patients achieving PASI 75 Mean change in PASI and BSA Changes in PGA Evaluation of adverse effects	**PGA response at week 12:** Higher (p=0.05) in tapinarof groups 65% - 1% b.i.d 56% - 1% QD 46% - 0.5% b.i.d 36%- 0.5% QD 11% - vehicle b.i.d 5%- vehicle QD **PASI 75 at week 12:** Higher (p=0.05) in tapinarof groups 65% - 1% b.i.d 56% - 1% QD 46% - 0.5% b.i.d 46% - 0.5% QD 16% - vehicle b.i.d 5% - vehicle QD **Mean reduction in %BSA at week 12:** Tapinarof group: 3.6%-4.9% Vehicle group: 1%-1.6%	Treatment-emergent adverse events 68% - 1% b.i.d 53%- 1% QD 58%- 0.5% b.i.d 45%- 0.5% QD 24%- vehicle b.i.d 26% vehicle QD Mild to moderate intensity Most common: Folliculitis , contact dermatitis,application site dermatitis, application site, irritation, allergic dermatitis, headache, monocyte count decrease (1 case in vehicle group) Discontinuation: 10% tapinarof groups 1% vehicle groups. Due to contact dermatitis and application site dermatitis.

Bissonnette et al. (randomized, double-blinded, placebo-controlled, phase IIa study, single centre)[2]	WBI-1001	61 patients aged 18-65 with: -Stable Plaque Psoriasis (≥ 6 months) -BSA ≥1% - ≤10 -PGA score ≥ 2-4 Randomized (2 : 1, 12 weeks, applied b.i.d): WBI-1001 arm (n=40) Placebo arm (n=20)	**Primary** Change in PGA score compared to baseline at day 84 **Secondary** Proportion of patients achieving at day 84: PASI50, PASI75 and PGA 0 or 1 Changes in BSA and PASI at day 84 compared to day 0	**Primary** Improvement in PGA score at week 12: WBI-1001 arm: 62.8% Placebo arm: 13.0% (P < 0.0001) **Secondary** **PGA 0 or 1** WBI-1001 arm: 67.5% Placebo arm: 4.8% (P < 0.0001) **BSA improvement:** WBI-1001 arm: -79.1%, Placebo arm: + 9.4% (P < 0.0001) **Change PASI from baseline at day 84:** WBI-1001 group: -71.0% Placebo group: -11.1% (P < 0.0001) **PASI 50:** WBI-1001 group: 72.5% Placebo group: 9.5% (P < 0.0001) **PASI 75:** WBI-1001 group: 50.0% Placebo group: 4.8% (P = 0.0004)	Treatment-emergent adverse events Mild to moderate intensity. WBI-1001 arm: 80% Placebo arm: 52.4% Hyperpigmentation, dermatitis, folliculitis, papules, pain and pruritus in the application site. Discontinuation: 2 patients from the WBI-1001 arm because of dermatitis and 1 patient from the placebo group due to a cerebrovascular accident

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