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HYPOTHESIS

New Antifibroblastic Medication in Dermatology: Could Nintedanib Treat Scarring?

Patricia Liana Cristodor[1,2,*], Alexandru Nechifor[3,*], Silvia Fotea[3,*], Thomas Nadasdy[2,4], Yousef Bahloul[2,5], Alin Codrut Nicolescu[6,*], Alin Laurentiu Tatu[3,4,7,8]

[1]Center for the Morphologic Study of the Skin MORPHODERM, University of Medicine and Pharmacy "Victor Babeș", Timișoara, TM, Romania; [2]Dermatology Department, Spitalul Clinic Municipal de Urgenta Timisoara, Timișoara, TM, Romania; [3]Clinical Medical Department, Faculty of Medicine and Pharmacy, "Dunarea de Jos" University, Galati, GL, Romania; [4]Multidisciplinary Integrative Center for Dermatologic Interface Research MIC-DIR, Galati, GL, Romania; [5]PhD Studies Department, University of Medicine and Pharmacy, Victor Babeș" Timișoara, Timișoara, TM, Romania; [6]Department of Dermatology, 'Roma' Medical Center for Diagnosis and Treatment, Bucharest, Romania; [7]Dermatology Department, "Sf. Cuvioasa Parascheva" Clinical Hospital of Infectious Diseases, Galati, GL, Romania; [8]Research Center in the Field of Medical and Pharmaceutical Sciences ReFORM-UDJ, Galati, GL, Romania

*These authors contributed equally to this work

Correspondence: Thomas Nadasdy; Yousef Bahloul, Dermatology Department, Spitalul Clinic Municipal de Urgenta Timisoara, str. Ofcea nr.24, Timișoara, TM, 300558, Romania, Tel +40 751609000, Email thomas.nadasdy@gmail.com; dr.yousef.bahloul@gmail.com

Abstract: There are a wide variety of disfiguring dermatological conditions whose pathologic substrate is represented by the unwanted deposition of collagen from dermal fibroblasts. Pirfenidone has demonstrated efficiency in the treatment of disordered collagen production when applied topically. Due to a similar mechanism of action, we also hypothesize that a similar medication, nintedanib, might have similar applications. We also propose that a liposomal technology may assist in the penetration of nintedanib and enhance its clinical effects.

Keywords: nintedanib, pirfenidone, keloid, scarring, fibroblast

Introduction

Scarring, keloids, systemic sclerosis, morphea, anetoderma, and cicatricial alopecia are all important disfiguring dermatological conditions in which direct inhibition of fibroblasts could provide a benefit. Pirfenidone, a direct anti-fibrotic agent recently approved for use in Idiopathic Pulmonary Fibrosis (IPF), has evidence demonstrating its effectiveness in dermatologic pathologies in which excessive fibroblastic activity is present. Indeed, this medication even comes in a gel formulation for topical use, but its availability is restricted to Mexico, which is the only country to have approved its use for the treatment of scarring. Available information is still in its early stages, but it is important to review the current data, rationale for its use, and the potential benefit it presents. We also hypothesize that a similar medication, nintedanib, might have similar applications.

Mechanism of Action of Pirfenidone

Pirfenidone ($C_{12}H_{11}NO$) is a small 0.185 kDa molecule consisting of a molecule of aniline that is bonded with an n-heteroarene ring at its n-side chain. Pirfenidone is metabolized via the P450 hepatic pathways into an active metabolite, 5-carboxy-pirfenidone. The majority of pirfenidone is then eliminated via the urine in this form, with only 1% being eliminated in its unconverted state. The half-time for pirfenidone is 2.4 hours, with 80% of the drug being eliminated within 24 hours.[1] Since this is a new medication, all the facets of its mechanism of action are not entirely described.

Pirfenidone primarily targets fibroblast cells. Under electron microscopy, the collagen fibrils deposited by isolated in-vitro fibroblast tissue stimulated with TGF-β1 are dense, unbranched, irregularly oriented, and have an average thickness of 225 nm. When samples were treated with pirfenidone, disruption of the normal fibrillar structure occurred. The fibrils

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became branched, shorter, and the average thickness was reduced to 75nm. Molecular analysis shows that pirfenidone reduces transcription of collagen I, III, V, and fibronectin I. However, transcription levels do not seem to correlate completely with protein deposition levels, with collagen III deposition levels even showing an inverse relationship. Pirfenidone appears to only be a direct inhibitor of collagen V. Collagen fibril formation, however, is delayed even in the absence of fibroblasts, which may account for this discrepancy.[2]

Outside of its direct role on collagen deposition, pirfenidone may also play a role upstream by downregulating the expression of ICAM-1 and directly inhibiting the production of TGF.[3,4] It may even play a double role in counteracting TGF-β's pro-fibroblastic effect by acting on distal molecular signaling targets (connective tissue growth factor, Akt, Smad3, p38, FHL2, Gremlin1, and CTHRC1). These molecules regulate fibrotic processes and are expressed by fibroblasts and other dermal cells. CTHRC1 inhibition may be one of the more direct and interesting targets proposed for pirfenidone, as this molecule has traditionally been thought to inhibit collagen matrix deposition. Recent evidence points to a more nuanced role for CTHRC1 in fibroblast migration and extracellular matrix contraction.[5]

Evidence of Pirfenidone's Use in Dermatological Pathologies

Pirfenidone's antifibrotic and anti-inflammatory effects are seen in both pulmonary and dermal fibroblasts.[6] Topical formulations decrease scar formation without an important impact on wound healing or infection.[7,8] Counterintuitively, pirfenidone may work to promote wound healing. Fifty-two patients with post-burn split thickness grafts were divided into two groups: 28 had their donor sites treated with pirfenidone gel under gauze, while 24 received gauze only. In order to verify how pirfenidone acts on epithelialization, biopsies from the donor sites were taken at day 10. The epithelial thickness was 98.21 ± 6 µm, compared to only 75.10 ± 60 µm in the control group ($p = <0.05$).[9] Whether this result was due to the pro-epithelializing effect of proper moisture control on wounds is unclear, but it does give evidence that pirfenidone is safe to use topically on wounds without the risk of excessive healing delays.

Established scars may also be reversed by pirfenidone. A controlled clinical trial using pirfenidone 8% topical gel applied t.i.d. on hypertrophic burn scars in a pediatric population of 33 patients was compared to a control group of 30 patients treated with pressure therapy. The Vancouver Scar Scale was used to evaluate the patients at 0 and 6 months. The majority of patients had a decrease of 30–45% in scarring compared to their baseline in the pirfenidone group in contrast to the 16% reduction in the pressure therapy group ($P < 0.001$).[10] The use of anti-fibroblastic therapy need not be limited to scarring, but can also encompass a wide range of therapeutic indications. A Phase II clinical trial of patients diagnosed with localized scleroderma treated with pirfenidone were followed over 6 months with significant histological improvement in atrophy, fibrosis, and inflammation. However, this trial suffered from a low sample number and a lack of a control group, and therefore further studies need to be done to recommend its use in scleroderma.[11]

A Proposal for Nintedanib for Topical Use

Nintedanib is a small molecule tyrosine-kinase inhibitor whose primary antifibrotic effects are through direct inhibition of VEGFR, PDGFR, and FGFR.[12] It is poorly absorbed via the gastrointestinal tract, and bound in high concentration to plasma proteins. It is degraded primarily by hepatic esterases (with only small fractions being converted via the cytochrome p450 pathways), and excreted through bile. Only small amounts are eliminated through the kidneys. While it has been approved for use in IPF, its use in skin pathology has not been fully studied; however, we propose that due to its similarities with pirfenidone, it could see similar applications.

Besides its upstream inhibition of the aforementioned growth factors, nintedanib may work in much the same way pirfenidone does: it disrupts collagen fibrils in cultured fibroblast cells but with a more pronounced effect and at lower concentrations. Nintedanib on cultured human pulmonary fibroblasts inhibits the transcription of collagens I, III, V, and fibronectin 1. In contrast to pirfenidone, nintedanib not only decreased protein levels of collagen V, but it also had an inhibitory effect on the synthesis of collagen I and III. It inhibits transcription and expression of plasminogen activator inhibitor 1, and thus can also be thought to have pro-fibrinolytic effects downstream of the serine proteases that modulate the extracellular matrix.

Furthermore, while pirfenidone does decrease fibronectin 1 mRNA, its effects on protein expression are less clear. Nintedanib, on the other hand, seems to decrease fibronectin 1 protein.[2] As such, nintedanib demonstrates similar, but

more potent, antifibrotic target effects when compared to pirfenidone. It not only decreases collagen production and disrupts fibril formation, but it seems to modulate, and in a sense, "weaken" the extra-cellular matrix holding collagen bundles together.

Nintedanib has also shown this anti-fibroblastic activity in human dermal fibroblasts. Scratch assays performed from cultured human dermal fibroblasts stimulated with TGF-B and PDGF showed delayed closure when exposed to nintedanib in a dose-dependent manner. The inhibitory effect of nintedanib in scratch assays was greater than that seen with selective inhibition of PDGFR, VEGFR, or FGFR alone. Furthermore, this same study demonstrates reversal of induced dermal fibrosis in bleomycin-injected murine specimens with decreased histological dermal thickness and decreased myofibroblast count after two weeks of nintedanib administration.[13]

We propose that nintedanib can be applied topically. It could potentially demonstrate local absorption through the epidermis due to its solubility in an acidic environment. This type of formulation may also circumvent the p-glycoprotein transport system that normally limits its oral absorption.[12]

Topical formulations that employ lipid nanocarriers may also enhance its absorption through the skin.[14] These formulations may use liposomes, polymeric nanoparticles, polymeric micelles, dendrimers, solid lipid nanoparticles, carbon nanotubes, quantum dots, or magnetic nanoparticles, and are especially appealing for topical application since lipid nanocarrier formulations have already been demonstrated to be beneficial in skin care.[15] They are used in a variety of topical treatments that require good penetration, including: alopecia areata, scleroatrophic lichen, lichen planus, scleroderma and rosacea.[16]

The temperature at which liposomes change state from solid to liquid is proportional to the saturation of their fatty acid chains. This often requires higher heat than that of ambient temperatures allowing for a controlled release when used on the skin. We propose a unilamellar liposomal formulation for nintedanib such as the one Tatu et al describe using the lipofilm method. This is both simple and can encapsulate medications with a variety of physicochemical properties, although lipophilic molecules such as nintedanib are preferred.[17] Delivery of nintedanib to affected skin using this method may lead to increased effects of the active substance, decreased systemic absorption, and it may also improve the skin's role as a protective barrier by acting as an emollient.

Data Sharing Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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