Original Investigation

Efficacy and Safety of Pirfenidone in Patients with Second-Degree Burns: A Proof-of-Concept Randomized Controlled Trial

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ABSTRACT

OBJECTIVE: Several studies suggest that pirfenidone may have a potential off-label use for wound healing. However, the effectiveness of this medication in patients with burns remains uncertain. Accordingly, investigators sought to assess wound re-epithelialization in patients with second-degree burns after adding pirfenidone to usual care.

DESIGN AND SETTING: Single-center pilot, proof-of-concept, single-blind randomized controlled trial.

PATIENTS AND INTERVENTION: Eight patients with second-degree burns were treated with occlusive hydrocolloid dressings and were randomly allocated to receive either no additional treatment or pirfenidone.

OUTCOME MEASURES: The primary outcome of the study was to evaluate wound healing between groups based on the thickness of the re-epithelialized epidermis at day 7. Secondary outcomes were to qualitatively assess the development of fibrotic tissue in the dermis, anomalies in the basal membrane, and the development of collagen fibers by histologic analysis. Liver and renal functions were measured daily to assess the overall safety of oral pirfenidone.

MAIN RESULTS: Patients treated with pirfenidone showed a remarkable improvement in wound re-epithelialization at day 7 (148.98 ± 13.64 vs 119.27 ± 15.55 μm; $P = .029$; 95% confidence interval, 4.14-55.29). Histologic evaluations showed less wound fibrosis in the pirfenidone group.

CONCLUSIONS: A decrease in wound healing time by enhancing wound re-epithelialization was observed with pirfenidone. Larger clinical trials are needed to reach more reliable conclusions.

KEYWORDS: burns, partial-thickness burns, pirfenidone, re-epithelialization, wound care, wound healing

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INTRODUCTION

Large split-thickness burns are considered critical wounds because they can cause serious hydroelectrolytic and metabolic alterations including fluid loss, electrolyte imbalances, and increased catabolism.[1,2] These conditions usually endure until complete closure of the wound is achieved. Therefore, rapid wound re-epithelialization is paramount for any burn treatment strategy. Current strategies involve a variety of dressings designed to provide a suitable environment for wound healing; however, these dressings are far from perfect.[3]

As part of efforts to find different approaches that improve wound re-epithelialization, several in vitro and animal studies have acknowledged the pivotal role of modulating the transforming growth factor β (TGF-β) family in wound healing.[4–6] The TGF-β family participate in the onset and development of wound healing by upregulating several inflammatory cytokines that eventually translate into wound re-epithelialization.[7–9] However, this relationship is often less straightforward than these results suggest. Several studies have demonstrated that overexpressing the isoform TGF-β1 plays a paradoxical nonlinear relationship in the recruitment of keratinocytes at the wound site.[10–12] This overexpression enhances the activity of fibroblasts and their conversion to myofibroblasts, causing wound constriction.[11,12] Therefore, an inflammatory state caused by a traumatic injury that spurs an overexpression of TGF-β1 may have a deleterious effect on wound re-epithelialization.[13] To try to counteract this effect, the US FDA has recently approved a TGF-β1 antagonist, pirfenidone, mainly for the treatment of pulmonary fibrosis.[14–18] Several studies have shown that pirfenidone has a potential off-label therapeutic use for wound healing based on its downward regulation of TGF-β1.[19–21]

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Although pirfenidone has a theoretical benefit, there is no actual evidence elucidating its effectiveness for wound healing in patients with burn injuries. Accordingly, this proof-of-concept randomized controlled trial was designed to determine the efficacy of pirfenidone for wound re-epithelialization in patients with burns.

METHODS

This study was a prospective, experimental, single-center, randomized, investigator- and outcome assessor-blinded pilot study with parallel groups to assess the efficacy of pirfenidone in wound re-epithelialization (an off-label indication) in patients with partial-thickness burns. This proof-of-concept study aimed to provide preliminary evidence of efficacy on a pathophysiologic mechanism: in this case, wound healing.[22] The study was performed at the Burn Unit of the Division of Plastic, Aesthetic, and Reconstructive Surgery of the Dr José E. González University Hospital in Monterrey, Nuevo Leon, Mexico. The study was designed and monitored in accordance with the Declaration of Helsinki and Good Clinical Practice as defined by the International Conference on Harmonization. The study was approved by the institutional ethics committee and registered at clinicaltrials.gov (NCT03530150). Data will be shared on reasonable request.

Between January and May 2017, patients between 18 and 60 years old with split-thickness burns less than 24 hours old were enrolled. Exclusion criteria were an age younger than 18 years, a history of allergy or adverse events with the use of pirfenidone, critical condition, inability to take oral medication, pregnancy, renal or hepatic insufficiency, or those with any medication or disease that would alter wound healing (eg, type 1 or 2 diabetes mellitus, systemic lupus erythematosus, a history of using steroids, rheumatoid arthritis, etc). Patients who dropped out of the study for any reason not related to their health condition or the use of pirfenidone were eliminated from the study. All patients provided written informed consent to participate.

Randomization, Allocation Concealment, and Blinding

Patients were randomly assigned (2:1) using a computer web program to receive either usual care or usual care and pirfenidone 600 mg. All personnel were blinded to allocation until patients consented to participate in the study. Patients and personnel in charge of providing medication and performing the procedures were not blinded. However, the principal investigator, the person in charge of gathering the biopsies and data, and the person who analyzed the data were blinded to treatment allocation.

Procedures

Pirfenidone was given orally once daily for 7 days. Burn wounds of eligible patients in both groups were treated throughout the study with hydrocolloid dressings (DuoDerm; ConvaTec, Bridgewater, New Jersey) and covered with sterile gauze rolls (Kendall Kerlix; Covidien, Dublin, Ireland). These dressings were changed every 3 or 4 days until complete re-epithelialization of the wound was achieved based on clinical evaluations. Wound re-epithelialization was clinically evaluated in both groups by one of two experienced plastic surgeons with extensive training in burn wound care. Further, biopsies of the wounds were taken from a representative zone at days 0 and 7 to evaluate the epidermis, dermis, basal membrane, and extracellular matrix histomorphometrically.

Primary, Secondary, and Safety Outcomes

The primary outcome of the study was to evaluate wound healing between groups based on the thickness of the re-epithelialized epidermis at day 7. Secondary outcomes were to qualitatively assess the development of fibrotic tissue in the dermis, anomalies in the basal membrane, and the development of collagen fibers with histology. Liver and renal functions were measured daily in the morning to assess the overall safety of oral pirfenidone.

Histologic and Histochemical Analysis

To obtain paraffin blocks, tissue samples were fixed with paraformaldehyde at 4% in a phosphate-buffered solution (pH 7.2-7.4). Afterward, histologic sections of 4 μm were obtained with a micrometer (RM2245; Leica, Wetzlar, Germany). Tissue samples were stained with hematoxylin and eosin to assess the general characteristics of the epidermis, dermis, and extracellular matrix. Van Gieson trichrome and Verhoeff stains were used to identify epithelial tissues such as collagen fibers and muscle fibers. Periodic acid-Schiff stain was used to evaluate the basal membrane.

Microscopic and Morphometric Evaluations

Microscopic high-resolution digital images were obtained with a light field microscopy with a Nikon Eclipse 50i (Nikon Instruments Inc, Melville, New York) and Digital Sight DDS-2Mu image analysis software (Nikon Instruments Inc). Epithelium thickness was determined by taking five measurements from the basal membrane to the stratum corneum between two dermal papillae to obtain a mean. If the stratum corneum was not available, the highest epidermal layer was used as the upper limit for evaluation.

Statistical Analysis

Descriptive statistics to show the population's characteristics and values were reported as frequencies (%) or mean ± SD. Researchers performed a Kolmogorov-Smirnov test to determine the normality of numerical variables. The χ^2 test for categorical variables and Student

t test for independent variables were used to determine any differences between the groups. A $P < .05$ was considered statistically significant, and a 95% confidence interval was used to determine effect size. All statistical analyses were performed using SPSS version 22 (IBM Corp, Armonk, New York), and graphics were designed using Microsoft Excel 2016 (Microsoft, Redmond, Washington).

RESULTS

Initially, 17 patients were assessed for eligibility. Of these, only 8 met the inclusion criteria and entered the study. All patients were evaluated, and there were no dropouts (Figure 1). Baseline characteristics are displayed in the Table. Overall, the majority of patients were men (n = 7, 87.5%), had a mean age of 29 ± 10.9 years, and had a total burn surface area (TBSA) of 35% ± 14.6%. Patients allocated in the pirfenidone group had a significantly lower TBSA compared with patients allocated in the usual care group (25% ± 6.1% vs 51.6% ± 2.8%; $P = < .001$). All other variables showed no difference between groups.

Primary, Secondary, and Safety Outcomes

Patients treated with pirfenidone showed a statistically significant difference in wound re-epithelialization at day 7 (14.98 ± 13.64 vs 119.27 ± 15.55 μm; $P = .029$; 95% confidence interval, 4.14-55.29; Figure 2). The newly formed epithelium in the pirfenidone group clearly displayed all epidermal layers (Figure 3). Conversely, patients in the usual care group showed a denser fibrotic tissue in their extracellular matrix, and the basal membrane was less evident and hard to identify (Figure 4). Clinical evaluations showed that wound re-epithelialization was achieved faster in patients treated with pirfenidone than in the usual care group (Figure 5). Throughout the study, there were no alterations in either liver or renal function.

DISCUSSION

The morphometric evaluations of the burns in this study showed that patients treated with pirfenidone had higher rates of re-epithelialization than those who received usual care only. This newly formed epithelium in the pirfenidone group displayed the complete spectrum of epidermal layers, which is a sign of a mature epithelium. Moreover, patients in the pirfenidone group showed a lower density of fibrotic tissue in their extracellular matrix, a finding likely attributable to the antifibrotic property of pirfenidone mentioned earlier. However, this determination was made by visual assessment of the epithelium only. Clinical evaluations of the wound also showed that patients treated with pirfenidone healed faster and more homogenously. Overall, it seems that the use of oral pirfenidone has a substantial beneficial effect on wound healing time of burns and an apparent effect on fibrosis in patients with burn injuries by inhibiting the TGF-β1 and ameliorating inflammation.

Several studies have demonstrated the effectiveness of modulating the TGF-β family for wound healing.[23–27] For instance, Singer et al[28] showed that inhibiting the TGF-β1 with a synthetic peptide in an animal burn model duplicates the re-epithelialization rate (90% vs 45%, $P = .002$) and substantially decreases wound contraction (35% vs 65%, $P = .02$). Although their study was performed on pigs, their findings align with this study because inhibiting TGF-β1 resembles the mechanism of action of pirfenidone, the medication used in this study.

The clinical improvement in wound re-epithelialization seen in this study is comparable to various studies that

Figure 1. STUDY FLOW DIAGRAM

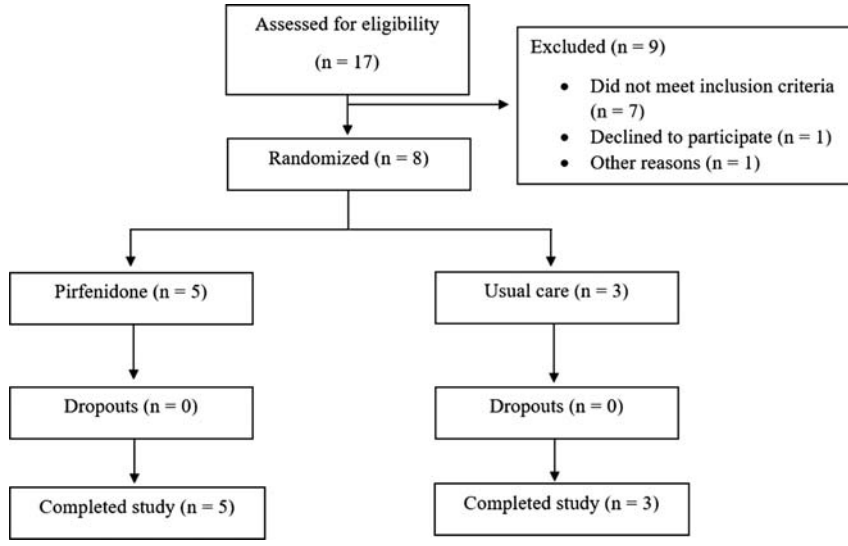


Table. BASELINE CHARACTERISTICS OF PATIENTS

Characteristic	Total (N = 8)	Pirfenidone (n = 5)	Usual Care (n = 3)	*P*
Male sex	7 (87.5)	4 (20)	3 (100)	.40
Age, y	29 ± 10.9	28.8 ± 11.34	29.3 ± 12.7	.95
Burn etiology				
Flame	4 (50)	3 (60)	1 (33.3)	
Electric	4 (50)	2 (40)	2 (66.7)	.46
Total burn surface area (%)	35 ± 14.6	25 ± 6.1	51.6 ± 2.8	<.001

Data are presented as frequencies (percentages) and mean ± SD.

evaluated the efficacy of pirfenidone in other wound types.[29] For instance, Janka-Zires et al[19] performed a randomized crossover study to determine the efficacy of topical pirfenidone in healing foot ulcers in patients with type 2 diabetes. This study found that patients receiving topical pirfenidone achieved a faster wound healing (52.4% vs 14.3%; $P = .02$) and a more pronounced reduction in ulcer size (100% vs 57.5%; $P = .01$) when compared with conventional treatment after 8 weeks.[19]

Similar findings were elucidated in a randomized, double-blind controlled trial published by Gasca-Lozano et al,[20] in which patients with foot ulcers were treated with topical pirfenidone and modified diallyl disulfide oxide versus ketanserin for 6 months. These authors found that patients receiving pirfenidone showed a statistically significant reduction in relative ulcer volume during the first 3 months when compared with their counterparts.[20]

Morphologic evaluations of newly formed epithelium in patients receiving pirfenidone showed a significant improvement in epidermal formation. These findings are congruous with that previously published by Mecott et al,[30] who demonstrated that split-thickness skin graft donor sites treated with pirfenidone had enhanced epidermal formation at day 10 compared with those sites that received usual care (99.52% vs 88.58%, $P < .05$). Interestingly, these results also suggest that pirfenidone may have a potential use in preventing pathologic scarring by ameliorating fibrosis at the wound site. However, this potentially beneficial effect should be considered with caution because of the lack of objective methods to evaluate fibrosis. Despite this, Armendariz-Borunda et al[21] showed that the administration of pirfenidone in hypertrophic burn scars improves several indicators of wound scarring.

Strengths and Limitations

This is the first study that evaluates the effectiveness of pirfenidone in wound re-epithelialization in patients with second-degree burns. However, there are several limitations that may reduce confidence in the results. First, the difference in TBSA between the groups is an important limitation. Further, because of the lack of placebo, the blinding of participants was unfeasible. Nonetheless, clinical and histologic evaluations were made by experienced

Figure 2. RE-EPITHELIALIZATION AT DAY 7

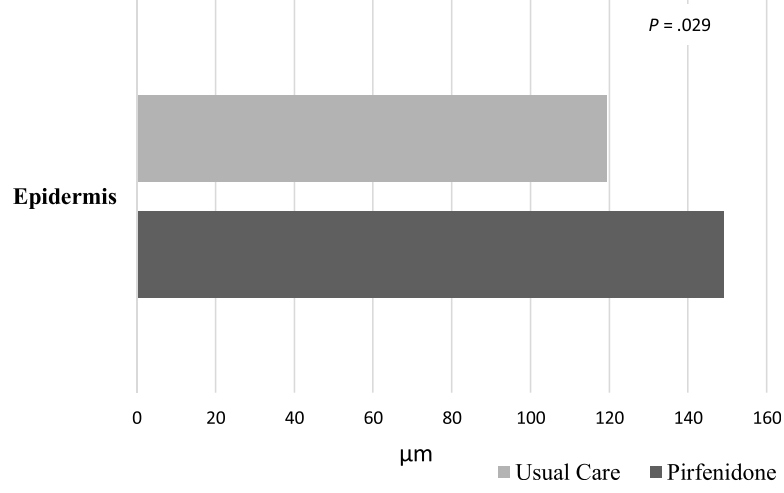
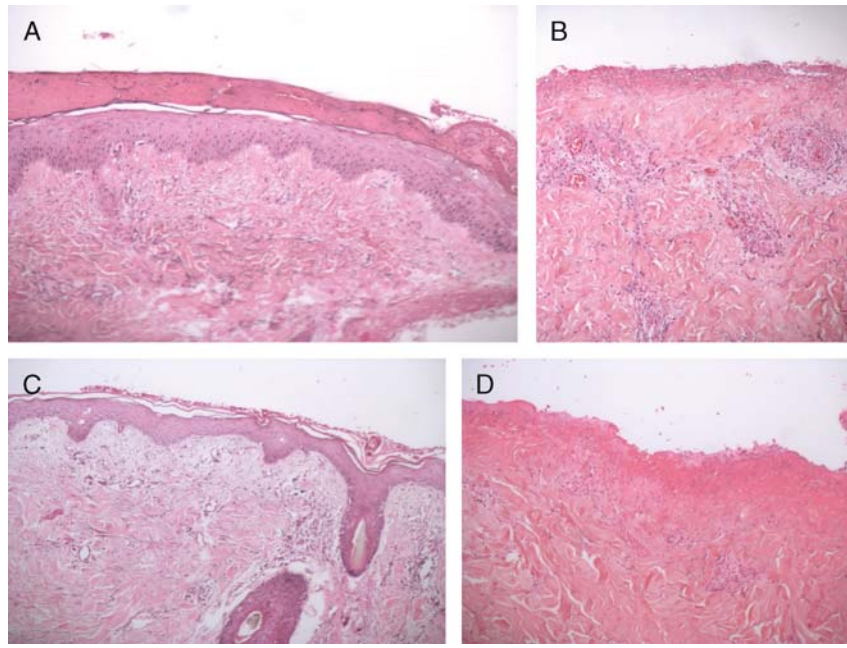


Figure 3. SKIN BIOPSY ON DAY 7

A and C, Pirfenidone group. B and D, Usual care.



personnel who remained blinded to treatment allocation throughout the study, a consideration that may outweigh this limitation.

It is also important to note that even though biopsies were purposefully taken from sites that represented the vast majority of the burn wound, re-epithelialization does not occur homogenously throughout the entire wound. These tissue samples therefore likely represent a "best case" sliver of the whole burn. However, the personnel who took the biopsies have extensive training in burn care and were also blinded to treatment allocation.

Finally, the number of participants was insufficient to draw reliable conclusions. Nevertheless, a statistically significant difference was reached, strengthening results.

Figure 4. HISTOLOGIC EVALUATION OF THE BASAL MEMBRANE AND DERMIS

A and C, Pirfenidone group. B and D, Usual care.

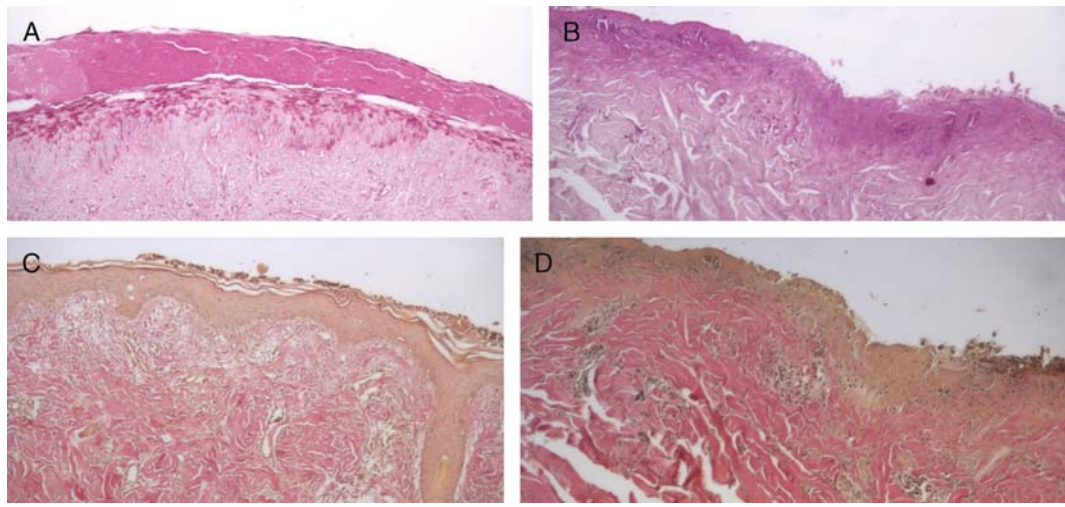
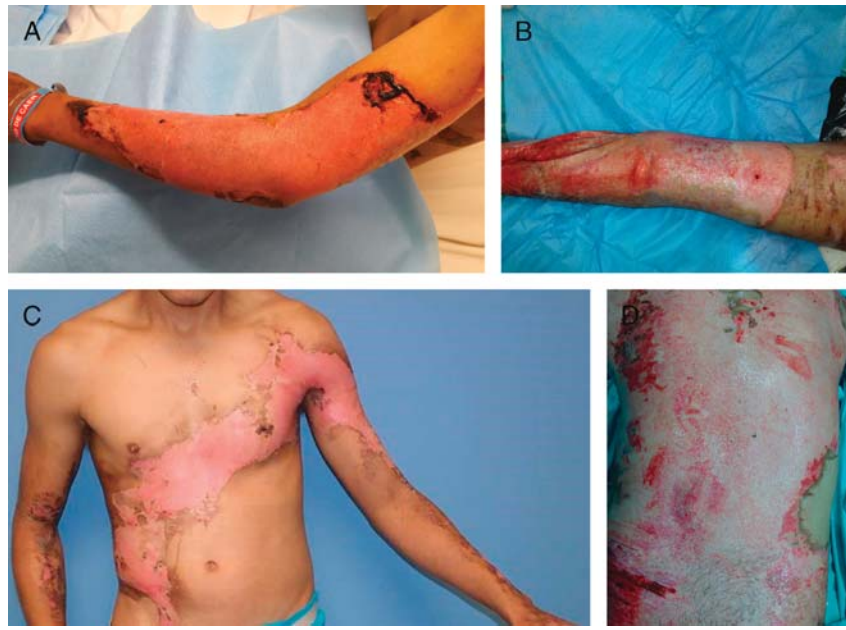


Figure 5. CLINICAL EVALUATION ON DAY 7

A and C, Pirfenidone group. B and D, Usual care.



Implications for Clinical Practice and Research

Wound care in burn patients involves a multidisciplinary approach to ensure rapid re-epithelialization and sidestep further complications.[31,32] Standard treatment consists of covering the wounds with a variety of available dressings;[33–35] however, this treatment requires constant dressing changes, which may further compromise skin re-epithelialization by tearing the newly formed epithelium, thereby prolonging patient's recovery, hospital length of stay, and the risk of infection.[36,37] Although newer dressings are designed to mitigate this issue, these dressings are not widely available and are expensive, which may be especially burdensome for patients with large burns. On the other hand, pirfenidone pricing varies among countries and laboratories. For instance, in several parts of the world, the price for a bottle of pirfenidone ranges from around US $8,000 to $10,000 per month,[38,39] whereas in other countries, such as where this study was conducted, the price ranges from US $400 to $500 per month. Based on this relative affordability and the results of this study, it seems that re-epithelialization in patients treated with pirfenidone could be achieved faster than with conventional treatment, decreasing healthcare costs for patients. These authors estimate that administering pirfenidone for 7 days would cost around US $500 to $600. That said, because the standard of care for patients with burns varies across healthcare institutions, this study cannot extrapolate costs to other institutions or assess the cost-effectiveness of results regarding the use of pirfenidone.

Regulating the expression of the TGF-β family has been of interest of late in wound healing research.[40,41] Previous literature acknowledges the role of activating or inhibiting the different isoforms of TGF-β in wound healing.[42–44] Thus, research has aimed to elucidate the potential role of modulating the TGF-β function with the use of pirfenidone to enhance wound healing.[20,28,29] The results of this study bolster previous evidence suggesting that pirfenidone may have an off-label therapeutic use for enhancing wound healing by modulating TGF-β. However, larger randomized clinical trials are needed to draw reliable conclusions more applicable to daily clinical practice. Also, future clinical trials should aim to determine the best combination of dressing and pirfenidone to provide faster wound healing and to objectively assess the potential therapeutic use of pirfenidone in wound fibrosis. Pirfenidone use also could be explored for other types of injuries or lesions that require enhancement of re-epithelialization and/or a decrease in fibrosis (eg, abdominal incisions, cosmetic surgeries, facial injuries, pressure ulcers, open heart surgeries, etc).

CONCLUSIONS

Wound re-epithelialization was accelerated by the systemic administration of pirfenidone. These promising

results need to be further supported with larger clinical trials to reach reliable conclusions about pirfenidone's effectiveness in wound healing. ●

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