LumiHeal® and Anti-inflammatory Regenerative Medicine (AIMED): a new management strategy for shortening wound healing and effective outcomes, from Repair 1.0 to Wound Regeneration 4.0

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Wound healing may require a long-standing period. As a result, patients, including their families and society, must sustain a relevant burden. Moreover, patients have to remain disabled also for a long time. Therefore, the healthcare service has to expend applicable costs. In the past, the Regeneration Medicine 3.0 represented the keystone for a holistic approach to wound management. However, there was also the need to consider the socio-economic impact on hospital costs and regional management spending review. Consequently, it is demanding to revise the care strategies for patients with skin wounds integrated into hospital-territory stewardship. In this regard, an innovative approach (Wound Regeneration 4.0) permitted to obtain exciting outcomes. Namely, an integrated protocol, combining anti-inflammatory, regenerative medicine, shortened the duration of wound healing, improved the quality of life of patients and family and significantly diminished the costs. In this context, the LumiHeal® gel associated with multi-LED light exerts a series of activities that actively promote wound healing. Moreover, LumiHeal® gel is active in all phases of wound healing and is effective on both chronic and acute wounds. The current outcomes suggest a multidisciplinary approach based on clinical, pharmacological, and economic issues that represent a point of departure for a new phase, such as the Wound Regeneration 4.0.

The Regenerative Medicine: a new approach

Patients with wounds require adequate attention and a thorough workup, mainly if they have complex treating lesions (1). Consequently, the repair, regeneration, and healing process are highly individual. In addition, the response singularity depends on specific immunopathological pathways. Therefore, regenerative Medicine is appropriate for managing wounds, mainly in complicated patients (2). Anyway, Regenerative Medicine relies on well-defined standards and protocols. We would report the personal experience in managing patients with wounds applying an innovative approach.

The patient with a difficult-to-treat lesion, such as a lesion that does not heal and progress throughout the normal phases of recovery (inflammation, proliferation, and remodelling), constitutes the paradigm of the chronic patient (no responders). The chronic patient is in the position of having to tackle and coexist with one or more diseases over time. This situation should be adequately managed to ensure an acceptable quality of life. In addition, chronic illness entails health economic aspects which are scarcely measurable, both considering the expensive materials and wound chronicity over time.

Notably, the care of chronic wounds accounts near

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4% of the total costs of the national healthcare service. The costs for wounds and lesions account for 15-20% for the dressing, 30-35% for personnel costs, and 50% for hospitalization. Expenditure is increasing seeing that to care for 2 million Italians with pressure wound affects public health costs for almost 1 billion euros a year.

The management of difficult-to-treat wounds in the outpatient setting requires close collaboration between the hospital and territory to guarantee clinical care continuity, even in light of the new LEA (essential levels of assistance) proposed by each Region in the new regional care pathways for chronic and sub-acute patients.

Clinical care continuity should be guaranteed everywhere. A possible solution could be to create *"integrated hospital-territory diagnostic-therapeutic pathways"* for treating all chronic diseases, in which a multidisciplinary network of professionals can make a difference in the management, evolution, and outcome of the injury.

The personal experience

The personal experience concerned an innovative model of care based on an original therapeutic approach to skin lesions, called AIMED (anti-inflammatory, regenerative medicine). This protocol is based on the circularity of the different phases.

The regenerative medicine outpatient clinic (RMC Regenerative Medicine Center) for recalcitrant lesions was established in the summer of 2015. This clinical project initially brought together professionals with different skills with a single mission: globally care for difficult wounds, involving patients and their families. Personal motivation was the main characteristic common to all project members. Each professional built a new organizational model and a close-knit network of activities with their essential personal expertise. Each member has embraced the philosophy of caregiving, associating respect for the clinical priorities of the patients and their families, adopting national and international methods and guidelines for wound management.

The clinical management includes assessment of the lesion, global evaluation of the patient, management and removal of the cause leading to the formation of the lesion, application of validated and shared protocols, prevention and management of complications, ultrasound treatment of skin lesions to remove necrotic and fibrinous tissue, acting as a bactericide and stimulating tissue regeneration, surgical procedures for biopsies, surgical debridement, and removal of lesions with reconstruction and/or skin grafts, documentation of the procedures through shared records, the definition of protocols based on technological innovations and biomarkers, consultancy and cooperation with other units (hospital, hospice, and primary care), and promotion of research and teaching on this matter.

According to international guidelines, the lesions are classified by type and stage, and the various types of advanced treatment are assessed and selected concerning the type of lesion and the operating protocol, with attention to pharmacoeconomic issues.

From repair to regeneration: Regeneration 3.0 phase

The RMC aimed to offer an innovative solution to the current difficulties in managing non-healing skin lesions. In the research progress, we defined *Repair 1.0*, meaning a dressing process involving advanced dressings. This type of dressing is required to maintain an adequate wound moisture level, be partly or fully occlusive, and passively absorb the exudate, with a function determined by the patient's metabolism and biological "performance."

Repair 2.0, in contrast, involves the use of bioactive dressings with a biological action on the wound (hyaluronic acid, collagen, silver, etc.). From this perspective, the RMC investigated a sterile gauze dressing with bioactive substances (hyaluronic acid, carnosine). Namely, persistent inflammation exerts a relevant role in non-healing wounds. In particular, nitric oxide contrasts the harm caused by ROS that, through systemic or topical treatment with antioxidants (carnosine), can be turned around in non-responding lesions (3). Moreover, bovine colostrum, at pH 6.8, acts against the tissue acidosis found in damaged tissues.

Regeneration 3.0 prioritizes combining the anti-inflammatory activity of the nine proteins acting as growth factors in the bovine colostrum, the homeostatic, angiogenic, and organizational activities of the matrix, the modulation of collagen synthesis,

and the remodelling of the epithelium. The choice of bovine colostrum relies on some properties: barrier action, anti-inflammatory action, pain relief, reduction and absorption of exudates, contrasting bacterial and fungal proliferation, antioxidant activity, hydration, and protection against skin diseases and dermatosis.

The RMC treats patients with chronic wounds of various aetiologies using the AIMED model. This method assures: i) optimal wound management with great awareness of dressing protocols and the use of medications existing on the market, integrated into the AIMED model; ii) a rapid healing, iii) a prompt pain relief, iv) reduced complications, v) reduced healthcare expenditure, vi) a better adherence and patient's and family's satisfaction, and vii) a reduced rate of recurrence. With the aid of the AIMED protocol, this study has tried to harmonize the clinical approach to the patient with skin lesions by putting him/her at the care core. However, difficulties may be found both in the hospital, where there is organizational excellence (at I, II, and III levels), and territory, where the patient often does not find adequate answers. In addition, during the Repair 1.0 and 2.0 years, the healthcare expense reached excessive levels regarding materials, aids, and devices to treat the wounds. However, there was no real action on the systemic and local processes that determined the onset of the lesion. The costs for the human resources also increased as the organization was dispersive. As a result, the only outcome was limited to maintaining a sterile dressing process but not decisive.

With the Regeneration 3.0 phase, a lot has changed regarding the healing rate. For example, the introduction of negative pressure wound therapy (NPWT) has radically accelerated the healing of complex lesions. However, the organizational difficulties persisted, mainly concerning territorial medicine. So that the NPWT may increase the costs if managed at the primary care level (for example dressing should be changed up to 4 days, often impossible in the doctor's office). For example, a lesion infected by *Pseudomonas aeruginosa* or *Escherichia coli* can significantly worsen the patient's local and systemic conditions. Thus, success can be wasted as a never-ending task when the management moves from the hospital to the primary care setting. Therefore, the need arises to reconsider the care model and propose a new, such as the Wound Regeneration 4.0, in which the international guidelines must be able to combine a reflection on the strategic choices for optimizing care with two main objectives: reduction of healing times, pain and reduction of both health and social costs (in both cases with benefits for the patient and his family). In this perspective, it seems strategic to reflect on the pharmaceutical equipment for outpatient clinics dedicated to the care and treatment of lesions.

Wound Regeneration 4.0 experience

The current study had the following objectives:

disseminating, among all professionals, the knowledge of innovative methodologies and protocols shared by the hospital network and territory, together with an analysis of clinical and economic indicators;

also guarantee to patients treated at home the bio-photonic system, shortening the healing time and hospitalizations so having a cost reduction, also for the integrated house assistance (IHA);

use a shared language for a correct management of patients with complex injuries;

create an integrated pathway between all health workers and embrace a new way of thinking that we could define;

reduce the burden on hospitals by avoiding the improper use of emergency and first aid services for patients who always more often use them because they do not find adequate responses at home and territory from well-trained and qualified personnel;

spread the organizational model to facilitate an interchange network with a rapid circulation of patients inside;

reduce the global healthcare spending on difficult injuries.

In the specific pathway of the patient (treated in consultation when hospitalized, then followed as an outpatient, and then managed at home), it has been reached the objective to demonstrate the importance of strengthening the management process when in the hospital there is the involvement of a specialized team that interacts with the department staff and broadens the skills and methodology transversally towards the patient. In order to reduce the healing time and social health expenditure, the bio-photonic system was

initially used by the RMC team, which involved and trained colleagues of the ward and emergency room in the immediate use of the LumiHeal® device (4).

We are convinced that biophysical therapies are essential because these natural resources, including light at various frequencies, really help the patient at a systemic and topical level. The Multi-LED KT-L Lamp is a certified CE marked class IIa electromedical device, emitting non-coherent blue light with a single peak emission wavelength between 440-460nm. The device was delivered to the CRM free of charge (a loan for use).

The protocol used at home was the same employed for outpatients. The medical and nursing staff of the hospital and territory shared and applied the home protocol twice a week for two months. In this period, there was a careful verification of the progress carried out by the CMR team, to guarantee the bio-photonic therapy even at home. The various phases of the protocol have been previously reported in detail (4). In particular, step 3 consisted of photobiomodulation (PBM), such as biophysical therapy. Namely, PBM is an adjuvant treatment for stimulating regenerative cellular processes, reducing inflammation and pain, and biochemical modulation of molecular response. In addition, PBM is particularly indicated in patients with difficult-to-treat wounds. In this regard, personal experience used the LumiHeal® protocol.

The LumiHea® protocol involves using the LumiHeal System comprised of two components: a non-coherent multi-light-emitting diode (LED) light source (primary device); and a topical chromophore-containing photo converter gel. The LumiHeal System produces fluorescent light energy (FLE), a form of photobiomodulation (PBM), to stimulate healing (4-9). The multi-LED light source delivers non-coherent blue light with a single peak wavelength between 440 and 460 nm. The LumiHeal gel, applied to a thickness of 2 mm, contains chromophores able to absorb the blue light emitted from the multi-LED light source and, through a Stokes shift, emit FLE in the range of 450-610 nm. Different wavelengths have different skin penetration capacities and are known to modulate the healing response (4-9). Treatment consists of using the multi-LED light to illuminate the LumiHeal Photo converter gel applied on the wound for the duration of the treatment, after which the multi-LED light is turned off, and the gel removed. The LumiHeal® method allows an effective and rapid improvement of treated lesions with pain reduction of the inflammatory process combined with other treatments (10) through the modulation of the immune response and cell proliferation (5). Moreover, in the immediate clinical course, the lesion changes in appearance at the biofilm level, at the bottom level of the lesion, and at the margins.

LumiHeal® a new frontier in wound healing

Lumiheal® is a photo converter used in combination with a LED lamp (KT-L or KT-P50) to heal acute and chronic wounds. It can stimulate mitochondrial biogenesis and modulate the three healing phases (inflammation, proliferation, and remodelling).

Photobiomodulation

Visible light has been historically used to treat a vast range of skin and soft tissue disorders and wounds. The therapy with light at a low energy level is effective as it exerts a stimulating activity on biological processes, such as the PhotoBiomodulation (PBM). The PBM rationale is that the photons activate endogenous photo-acceptors that induce a cascade of molecular events (11,12). Usually, PBM techniques include low-level laser, LED, and broadband light lamps. The PBM therapy positively affects all phases of wound healing, including the growth of granulation tissue, collagen synthesis, and nitric oxide, acting as an anti-inflammatory agent and pain-reliever (13).

The biomodulation by fluorescent light energy (FLE) is a form of PBM type that can stimulate mitochondrial biogenesis (14). FB Dermatology Srl introduced the patented system, known for its emitted blue light and FLE to penetrate the skin and promote wound healing (15, 16).

A peculiarity of LumiHeal® is its capacity of acting on every phase of the healing process. LumiHeal® can have chronic wounds progress out of their stalled, chronically inflamed status and respond to treatment like acute wounds would do. Namely, the preclinical data demonstrated that PBM modulates the wound healing process. LumiHeal® gel re-activates the healing of difficult-to-treat wounds and

acute wounds, including traumatic wounds, surgical wounds, burns, sutures, and skin grafts. In particular, LumiHeal® gel induces cellular proliferation, promote the synthesis of healing proteins, increases collagen production, stimulates angiogenesis, relieves pain, and physiologically remodels the collagen.

The indications of LumiHeal® gel are chronic wounds (i.e., venous ulcer, diabetic foot, pressure ulcer, and ischemic ulcers); acute wounds (i.e., burn, post-surgical wounds, and trauma); and cosmetics (cosmesis for scars). The contraindications include photosensitivity, pregnancy, breastfeeding, and childhood). The first effects can be observed after 15 days, or in any case, a mean 50% reduction of wound area is usually observable after 4-6 weeks.

Clinical records

The last experience included 2836 patients visited in a 5-year timeframe (Fig 1-5). In particular, the national healthcare service reimbursed 2154 patients (assuring 4067 performances), whereas 682 (with 967 performances) were private patients. Vascular lesions accounted for 72% of the global sample, rheumatological lesions for 5%, and bedsores for 23%.

Pharmacoeconomic outcomes

The global cost for the supply of LumiHeal® and medical devices was 21.272 %; in the graduated scale, the income deriving from the regional reimbursement was 75.782%. Thus, the gross operating revenue was 54.509 % for the hospital organization. Moreover, the advantages for the patients, and indirectly for the society, were also more significant. The 62% of patients with non-responder wounds obtained a 50% reduction of lesions within three months. Furthermore, a complete recovery was observed in 18% of patients with non-responder wounds within three months.

The global saving is impressive if it is considered a series of direct and indirect costs. Even if a precise estimate is not possible as many variables have to be considered, the mean cost for a hospitalization day may be more than €1000. The cost of a day job is about €200. Moreover, medications, rehabilitation, transportation, and company costs may be costly, mostly in severe patients. Last but not least, the quality of life and wellbeing, also of the family, have a considerable burden. Therefore, this new approach could guarantee great savings and a significant improvement for the people.

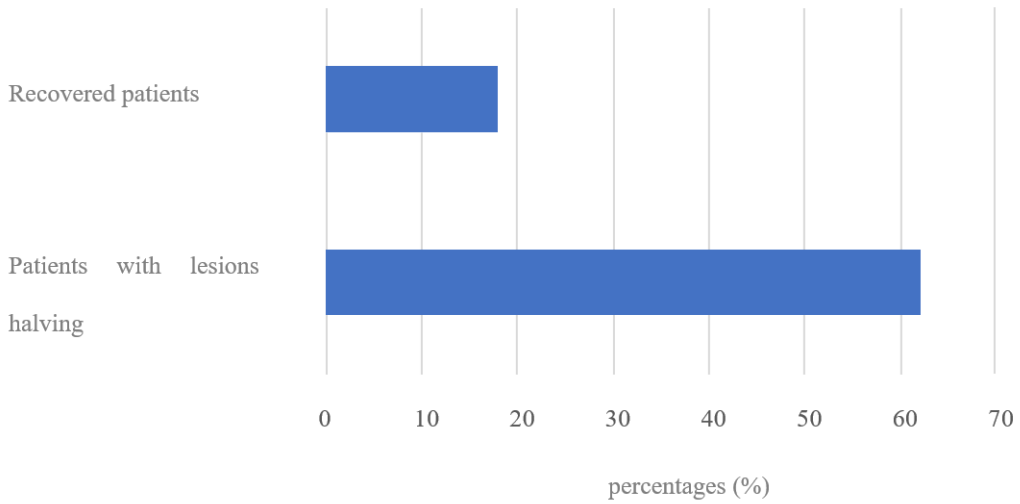

Fig. 1. *Pharmacoeconomic outcomes obtained in patients treated with Regeneration Medicine 3.0 protocol after 3 months*

Recent findings

In February 2020, shortly before the start of the COVID-19 pandemic, results of the clinical activity of the RMC were reported in a Plenary of the Hospital group ("Regenerative medicine: the patient with disabilities at the centre of care").

The analysis covered the three-year activity, detailing the number of patients enrolled, services reimbursed by the national healthcare service (NHS), insurance premium, or freelance work. In addition, the report described the cost analysis performed by the competent offices and the ongoing evaluation of economic performances. In particular, biophysical therapies, mostly Lumiheal®, were evaluated in terms of expenditure/revenues and potential savings of healing times and the use of additional materials for complete healing. The Key Performance Indicators (KPI) were:

a new consideration of RMC that went beyond the concept of the classic outpatient clinic but could share clinical experiences with the best technologies and be the reference for the patient and family;

a replicable and effective methodology;

the divulgation of methodology;

the need for clinical and economic outcomes;

an accurate data evaluation according to the RMC strategy;

an appropriate and responsible management of KPIs

a communication about KPIs and how they can help us change performance

a dialogue with the Purchasing Department for the budget definition;

the use of cutting-edge technologies and innovative therapeutic approaches to reduce healing times;

a direct relationship with GPs and IHA to rationalize home management with a reduction in healthcare expenses for the NHS.

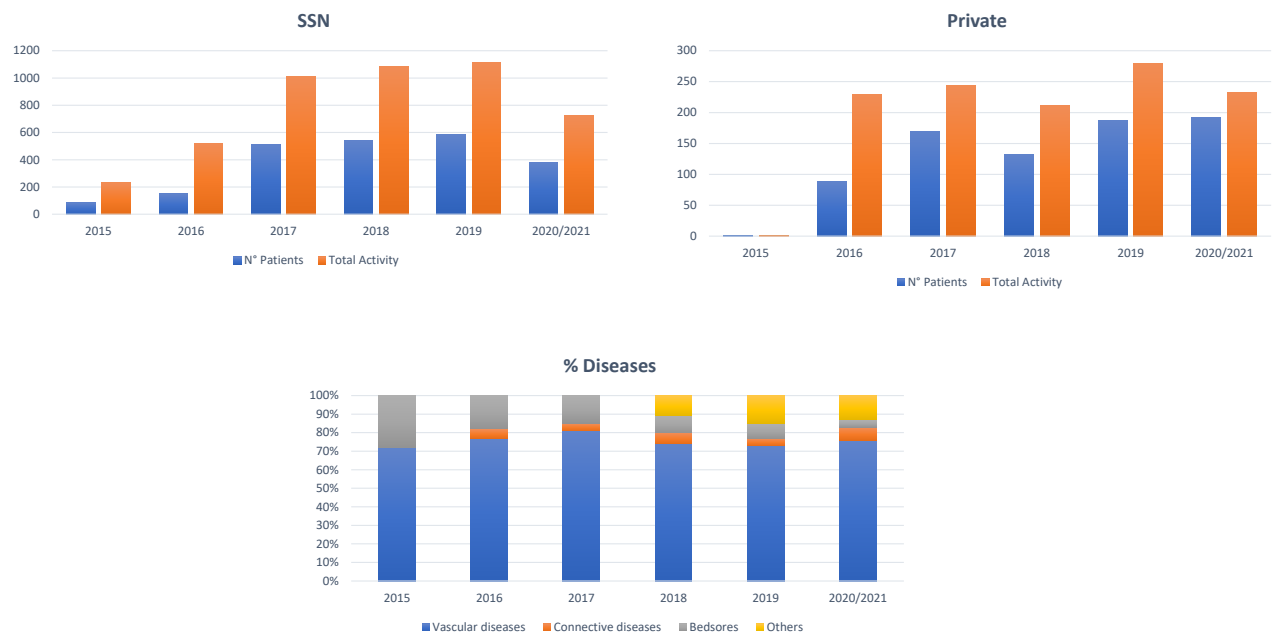

Fig 2. *Number of treated patients and performances during some years SSN and Private and types of diseases.*

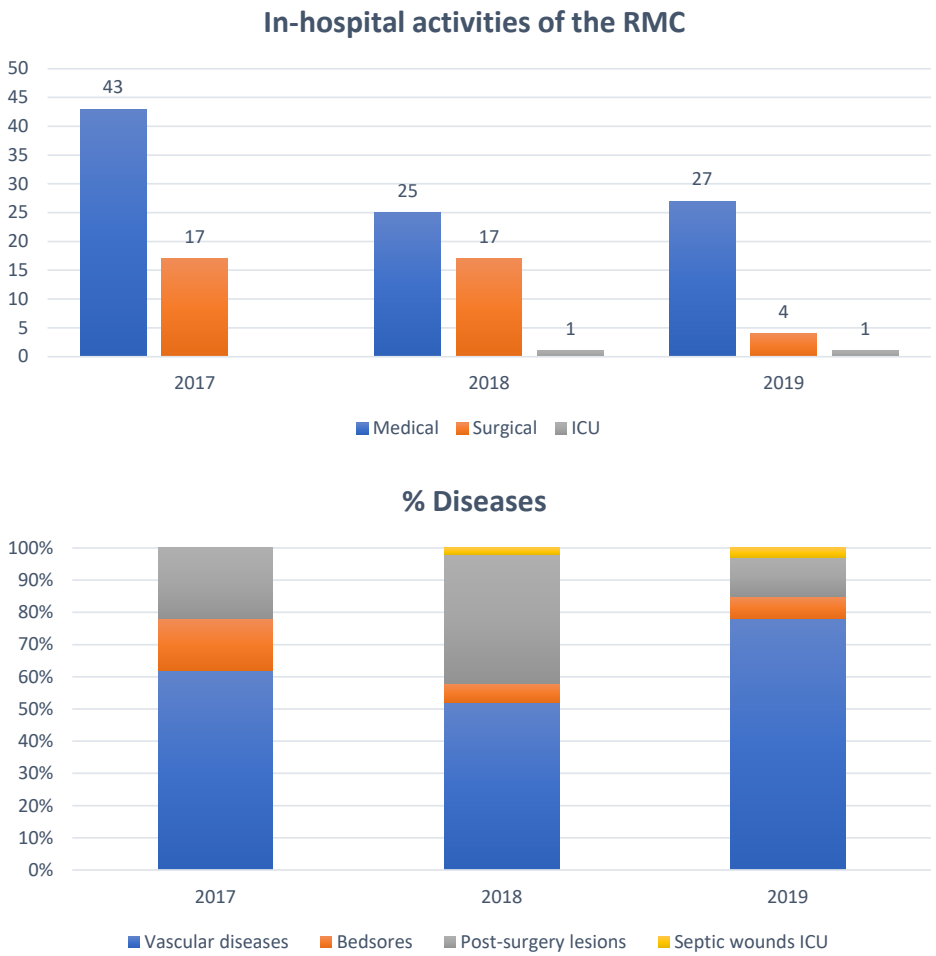

Fig. 3. *The number of patients and activities considering different conditions.*

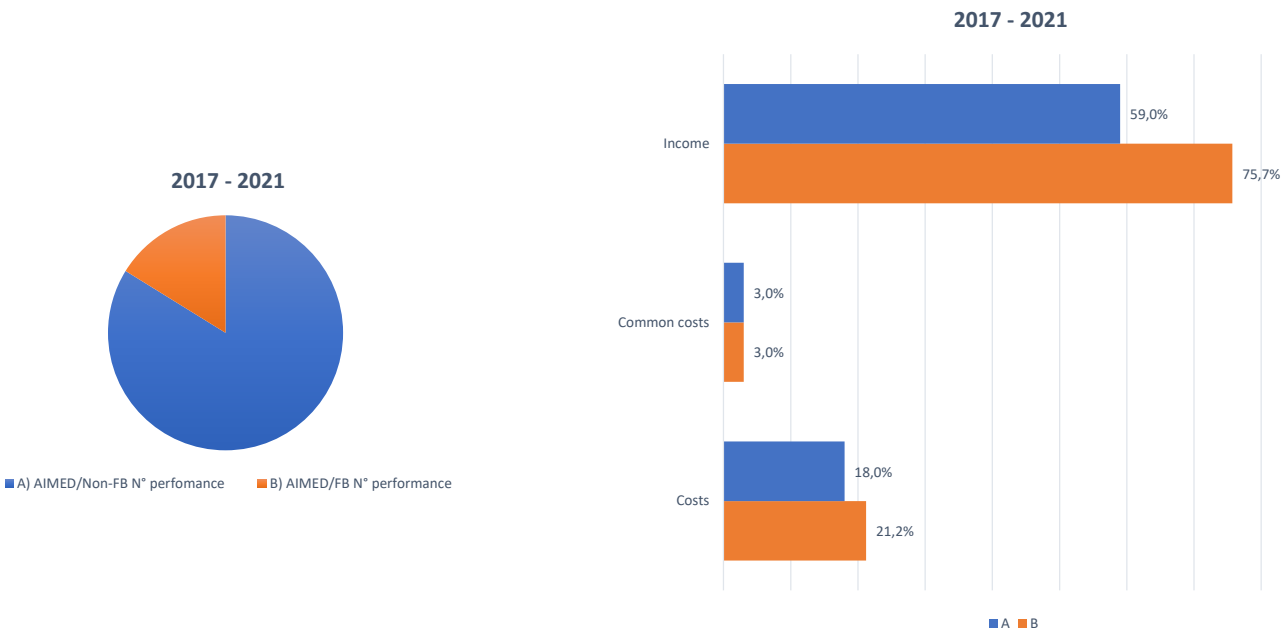

Fig 4 . *.The number of patients and activities considering different conditions AIMED /non FB VS AIMED/ FB.*

The last outcomes

The COVID-19 pandemic significantly affected the care for the other diseases and had a relevant impact on psychological issues. In this context, the present experience demonstrated that the new technology with bio-photonic therapy could also be applied at the primary care level, mainly concerning home care. Namely, the biophysical therapy had an excellent clinical performance due to the results obtained about the healing time and reduction of complications.

The cost/income analysis allowed an engaging projection on the savings for the GP concerning the reduction of the global costs for materials and better performance on the total number of hospital admissions (- 30/33%) and on working days lost (-23/32%) in working patients. In addition, the recovery time diminished and material and staff costs (Figure 1). In particular, figures 2, 3, 4 and 5 detail the pharmacoeconomic issues in patients cured with different protocols. The cost-saving, clinical improvement, and pain reduction were relevant as reported. So, this experience demonstrated that the management of chronic patients could be guaranteed along the entire pathway from hospitalization to the outpatient clinic, primary care setting, and at home. As a result, this protocol ensures personalized medicine to reduce inconvenience for the patient and the family.

CONCLUSION

The wound healing process is a complex process intertwined with the biological mechanisms causing individuals to become ill. In addition, systemic and local factors combine to cause the process to become chronic and perpetuate itself in the skin wound, an expression of it all. Regenerative Medicine provides

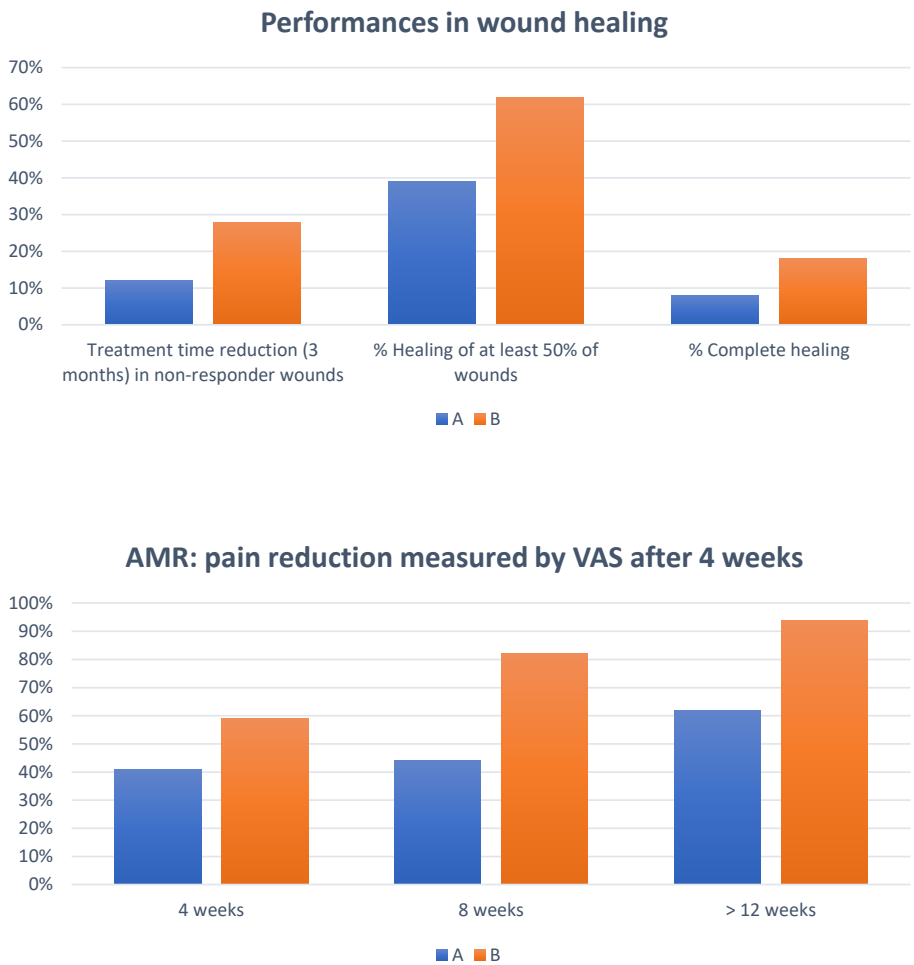

Fig. 5. *Results on wound healing rate and pain reduction*

new approaches to manage wound healing, mainly concerning difficult to treat lesions. An innovative protocol using multidisciplinary management and original medical devices, including the LumiHeal®, allows achieving relevant savings and optimal patient care. The Wound Regeneration 4.0 ensures an optimal pharmaceutical expenditure and pays attention to technological innovations supported by documentable results on clinical efficacy, healing speed, and spending review. The LumiHeal® technology and method play a major role in determining a treatment protocol for chronic non-responding skin lesions for the near future.

Conflict of interests:

All authors state that there is no conflict of interest.

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