

Plasma-activated hydrogel as a Vitiligo Therapy: Clinical Experiences

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Cold atmospheric plasma (CAP) is known to possess diverse therapeutic properties, for example antibacterial, antitumor, and regenerative, in a dose and species-dependent manner.¹ Their significance has been substantiated by efficacy and safety established in more than ten human clinical trials for treatment of chronic wounds² and surface tumors.³ However, its translation potential is often perceived as limited by, for example, large variation in CAP properties by conditions and surface topology of living tissues potential translational barriers of exposing high energy ions and electrons to human, and the lack of CAP device standardization. It is therefore highly desirable to seek technology innovations that can overcome the above challenges.

Recent studies of plasma-activated water (PAW) illustrate the feasibility of injecting PAW to the site of a target tissue (e.g. a solid tumor), although these studies are relatively recent with little understanding of, for example, how reactive species in PAW are maintained without losing their activity via recombination reactions and without migrating to non-targeted tissue areas. Further, most current studies of plasma-activated water or culture media are done in vitro or in animal models that are not necessarily relevant to the target disease. As a result, clinical viability of PAW remains a theoretical possibility and its impact is yet to reach the communities targeted by plasma medicine (e.g. clinicians, patients). Historically, clinical acceptance and widespread utility can take many decades, for example the photodynamic therapy has become a clinical option only in recent 10-20 years despite its efficacy being reported more than 100 years ago.⁴

Here, we report, for the first time, an investigation study with laboratory animals and a randomized controlled trial of human patients of plasma-activated hydrogel (PAG), in the form of cream, as a therapy for vitiligo.⁵ This is an incurable autoimmune disease that affects 0.5-2% of world population with severe psychological consequences and socioeconomical implications. We show that plasma-activated hydrogel is effective in reducing or removing vitiligo lesions with little sign of reoccurrence in a clinically relevant mouse model and somewhat surprisingly its efficacy appears modestly better than CAP itself. In human patients with focal vitiligo, PAG treatment achieves full and partial recovery from 20% and 80% of vitiligo lesions in a randomized and controlled clinical trial (RCT) of human patients. No recurrency is observed in a follow-up period of 6-18 months. In terms

of mechanisms, our results with the mouse model show that PAG acts on multiple targets important to vitiligo pathogenesis, including the infiltration of CD3⁺ and CD8⁺ T cells, the expression of transcription factor NRF2, and the activity of inducible nitric oxide synthase (iNOS).⁵ Together, PAG activity on these multiple targets help suppress and prevent the uncontrolled attack of T cells on skin melanocytes, the key of the vitiligo pathology.

As a common practice with clinical studies, we address potential limitations of our RCT. First, the sample size is 20 patients with a total of 40 vitiligo lesions, and with statistical significance. It is desirable to extend this to include larger patient populations. Second, our follow-up period is varied due to insufficient patient compliance – patients tend to get on with their lives without returning to their clinic if their conditions are under control. It would be useful in further randomized controlled trials to facilitate a prolonged follow-up period to quantify the existence and frequency of disease recurrence. Finally, this study addresses focal vitiligo. It will be of interest to test PAG in other types of vitiligo.

In summary, this work demonstrates two breakthroughs in clinical feasibility, firstly PAG as an effective therapeutic with straightforward translation pathway and secondly PAG as a route to treat autoimmune diseases. At present, vitiligo is treated with immunosuppressive drugs, that are associated with significant side effects and too expensive, and/or with specialized UV therapy that requires frequent hospital visits, both with clear risk of recurrence. Significantly, these therapeutic options are not accessible to patients living in rural areas or developing countries. PAG, in the form of cream, can be administered readily by non-physicians, including patients and their relatives. More studies are therefore warranted.

References:

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