Efficacy of platelet-rich plasma in combination therapy for vitiligo

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Abstract

Vitiligo is a recalcitrant, disfiguring autoimmune disorder resulting from the loss of epidermal melanocytes. Many therapeutic approaches have been used with various outcomes. Platelet-rich plasma has recently been an alternative treatment in numerous skin disorders, including vitiligo. This study aims to evaluate the efficacy of platelet-rich plasma modality as an adjunctive therapy for vitiligo. A search of clinical studies in human was conducted in the PubMed, Cochrane and Scopus databases with specific MeSH term (Medical Section Heading) terms. All data analyzing and grouping are performed with STATA version 14.0 (Stata Corp LP, College Station, TX). Total seven manuscripts met with the study inclusion criteria and were included in this study. Combination therapies rather than treating with monotherapy were proved for getting better repigmentation and outcomes. In vitiligo, platelet-rich plasma (PRP) used as an adjunct therapy related with other standard modalities compared with PRP alone or other control group, there was clinically as well as statistically significant in repigmentation. PRP therapy is generally considered as safe apart from minimal side effects like pain, erythema and minor complications for short duration immediately after procedure. In conclusion, a novel autologous therapeutic modality, PRP therapy with high concentration of growth factors tends to skin repigmentation in vitiligo as adjunct therapy for standard vitiligo treatment. However, larger population with longer duration clinical trials are necessary to measure the exact efficacy and mechanism of PRP on vitiliginous skin.

Keywords: *Vitiligo, Platelet-rich plasma, Combination therapy*

1. Introduction

Vitiligo is an autoimmune disorder leading to unpredictable loss of epidermal melanocyte with symptomatic depigmentation which affects the individual self-esteem and dermatological quality of life index. Prevalence rate was 0.5-2% related with geographic variation regardless of races and sex. (Rashighi & Harris, 2017) Platelet-rich plasma (PRP) is derived from autologous venous blood with growth factors in platelets of plasma concentrate which promote the activation and stimulation of epidermal keratinocyte and melanocyte. Regards to polygenic nature of vitiligo, some facts pave the way for better responses with PRP as adjunctive treatment rather than monotherapy.

2. Objectives

The objective was to evaluate the efficacy of platelet-rich plasma as an adjunct therapy for vitiligo.

3. Materials and Methods

All studies were systematically searched is based on the Cochrane Highly Sensitive Search strategy according to Cochrane Handbook for Systematic Reviews of Interventions version 6.0, updated July 2019 (Higgins JPT, Cochrane, 2019) from Pubmed, Cochrane and Scopus online databases with MeSH (Medical Section Heading) terms ;((“vitiligo” OR “leukoderma”) AND (“platelets” OR “platelet-rich plasma” OR “platelet gel” OR “platelet-rich fibrin” OR “platelet-releasate” OR “PRP” OR “leukocyte platelet plasma” OR “LPRP” OR “L-PRP” OR “LPRP gel” OR “leukocyte and platelet-rich plasma gel” OR “pure platelet-rich plasma” OR “P-PRP” OR “PPRP” OR “advanced platelet-rich plasma” OR “advanced PRP” OR “A-PRP” OR “APRP” OR “autologous cells” OR “plasma rich in growth factors”);(“Clinical trial”; “Full text”; “Human”; “English”)) to identify the selective inclusion criteria up to April 7th , 2020.

Studies with non-human trials, case reports, review articles, conference proceeding reports, clinical trials concluded with non-extractable data and limitation of full text assessment will be excluded. All data were analyzed and grouped with STATA version 14.0 and Review Manager 5.3 (Rev Man). Outcome measurement were done with repigmentation scale by investigators’ global assessment and visual analogue scale according to patients’ subjective score.

4. Results

Total potential 263 studies identified through Pubmed, Cochrane and Scopus online databases. Among these, 126 articles are left after removing duplication and irrelevance studies 104 were excluded after reviewing the abstract of these studies according to Cochrane Handbook for Systematic Reviews of Interventions version 6.0, updated July 2019. (Higgins JPT, Cochrane, 2019) Finally, seven studies are eligible for qualitative analysis, compatible with study inclusion criteria and summarized in the table 1.

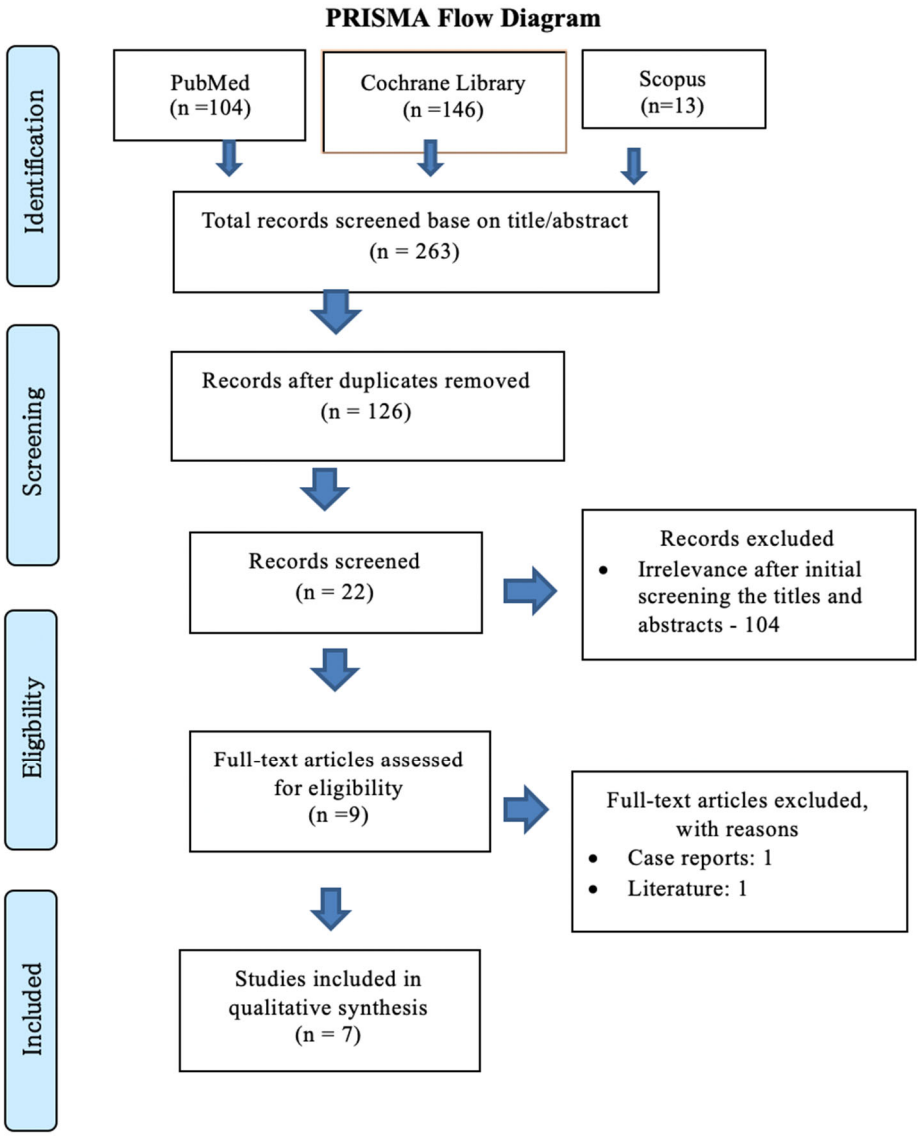

Figure 1 Study selection flow chart for platelet-rich plasma combination therapy for vitiligo

Table 1: Characteristic of included studies

Study, Year	Study Design	Vitiligo Subtype	Participants			
			No. of patient /patch	Mean age±SD (year)	Skin type	Mean disease duration±SD (month)
Combination of PRP with laser and light-based treatment in vitiligo						
(Kadry, Tawfik, Abdallah, Badawi, & Shokeir, 2018)	RCT, NB, WP	Stable NSV	30 pt/ 120 pc	32.03±12.29	II, III, IV	22.53±23.75
(Abdelghani, Ahmed, & Darwish, 2018)	RCT, parallel groups, NB	Stable NSV	80 pt	34.90±15.39 33.90±11.89 36.95±13.04 29.60±10.80	III, IV	NA
(Ibrahim, El-Ashmawy, El-Tatawy, & Sallam, 2016)	WP, NB	NSV	60 pt	28± 5.56	III, IV	5.9±6.2
(Khattab, Abdelbary, & Fawzi, 2019)	RCT, single blinded	Stable NSV and segmental, symmetrical	52 pt	25.42±7.60 24.9±5.60	III-IV	NA
Combination therapy of PRP with local and systemic therapy in vitiligo						
(Saify, Gupta, & Sharma, (May. 2019))	RCT, NB	NA	120 pt	31.96 ±11.60	NA	NA
Use of laser with PRP in vitiligo surgery						
(Garg, Dosapaty, & Arora, 2019)	NB, WP	Stable vitiligo	10 pt / 20pc	NA	IV	NA
(Parambath, Sharma, Parihar, Sahni, & Gupta, 2019)	WP, double blinded	Stable NSV and segmental	20pt /40 pc	23.1± 7.6	NA	NA

NSV = non-segmental vitiligo, NA = not available, NB= non-blinded, RCT=Randomized Comparative Trial, WP=within patient.

Combination of PRP with laser and light-based treatment

Total 2 articles examined the effect of PRP with fractional carbon dioxide (CO2) laser including control group. (Abdelghani et al, 2018; Kadry et al, 2018) Different method of PRP preparation in each study but the same mode of PRP used. 110 vitiligo subjects having PRP alone, laser monotherapy and combination therapy then compared with control groups. In outcome measurement, there was variable improvement in each group. However, laser and PRP combination and PRP monotherapy achieved significant outcome in repigmentation and reduction of vitiligo surface area as well together with minimal side effect like pain.

Another article studied with Narrow band ultraviolent B (NB-UVB) therapy combination with PRP therapy, one study compared combination laser with NB-UVB and laser monotherapy as well as PRP monotherapy with 80 adult vitiligo patients. (Abdelghani et al, 2018). Among four different intervention group, the mean ranking for repigmentation in each group was 63.40 in laser and PRP combination group, 39.70 in laser and NB-UVB group, 31.65 in laser monotherapy and 27.25 in PRP alone group. Furthermore, in NB-UVB combined with PRP injection compared with NB-UVB monotherapy in 60 vitiligo subjects.(Ibrahim et al, 2016) There was significantly increase in qualitative response 55% excellent in PRP side compared with control which is 0% in response. Similar study with excimer laser for monotherapy and combined with PRP in 52 vitiligo patients. (Khattab et al, 2019) PRP as adjunct therapy (PRP and excimer laser) resulted excellent response 34.6%, 50% of patients had good reaction and 15.4% had no reaction compared with laser alone which was 0% in excellent result. Therefore, PRP and laser therapy had highest repigmentation outcomes than laser alone. However, there was mild tolerable pain for PRP injection and recovered a few minutes after treatment.

Combination therapy of PRP with umbilical cord blood in vitiligo

One study did open prospective trial in 120 vitiligo patients to evaluate PRP and umbilical cord blood (UCB) therapy.(Saify et al, (May. 2019)) Different treatment groups with local PRP application, systemic PRP/Single donor platelet intravenous transfusion, intravenous UCB transfusion in separated groups as control. 60% of patients with combined I/V UCB and local PRP injection got maximum response, achieved repigmentation in more than 2/3rd of depigmented area.

Table 2: Studies with vitiligo intervention and outcome measurement

Author, Year	Intervention – number of patients/patches	Outcome Measurement (n)			P value
		VAS (Mean±SD)	Repigmentation> 75% (Percentage)	Repigmentation >50% (Percentage)	
Combination of PRP with laser and light-based treatment in vitiligo					
(Kadry et al, 2018)	PRP alone- 30 pc	6.67±2.37	NA	NA	<0.001
	PRP+FxCO2 - 30 pc	6.87±2.65			
	FxCO2 alone - 30 pc	4.87±2.19			
	Control - 30 pc	1.30±1.91			
(Abdelghani et al, 2018)	PRP alone – 20 pt	3.85±3.68	20	NA	0.025
	PRP+FxCO2 – 20 pt	8.2±0.616	40	60	0.001
	FxCO2+NBUVB – 20 pt	5.56±3.42	5	25	0.062
	FxCO2 alone– 20 pt	4.50±2.76	10	NA	0.037
(Ibrahim et al, 2016)	PRP + NBUVB–Rt side (60pt)	NA	55	20	<0.001
	NBUVB alone – Lt side (60pt)		0	0	
(Khattab et al, 2019)	PRP + Excimer laser – 26pt	10±0.41	34.6	50	0.000[a] (HS)
	Excimer laser alone- 26pt	0	NA	34.6	
Combination therapy of PRP with local and systemic therapy in vitiligo					
(Saify et al, (May. 2019))	IV PRP + local PRP – 20pt	NA	30	50	NA
	IV CB + I/V PRP – 20pt				
	local PRP– 20pt		60	30	
	IV CB only– 20pt		50	30	
			40	40	
Use of laser with PRP in vitiligo surgery					
(Garg et al, 2019)	PRP suspension+ Er: YAG – 20pt	NA	80	10	NA
(Parambath et al, 2019)	PRP – 20pt	NA	80	NA	0.001
	Control – 20pt		55		

VAS= visual analogue scale (0- 10 points, 0 = not satisfied at all, 10= totally satisfied), FXCO2= fractional carbon dioxide laser, CB= cord blood, HS= highly significant, NSV= non-segmental vitiligo, NA= not available, pt=patients, pc= patches, [a]= statistical significance.

Use of laser with PRP in vitiligo surgery

In 1952, several surgical modalities are introducing as alternative therapy for stable vitiligo.(van Geel, Ongenae, & Naeyaert, 2001) Among them, non-cultured epidermal suspension (NCES) transplantation is successful in repigmentation in two clinical trial. Total 21 NSV patients, single session with NCES suspended in PRP compared with control, suspended in phosphate buffered saline (PBS).(Parambath et al, 2019) In that study, PRP arm were better result 75.6% repigmentation at 6month with p value of 0.0036. Repigmentation resulted between PRP arm and non PRP arm showing statistically significance at 6month follow up. Another study was using PRP and 2940-nm ablative Erbium yttrium aluminium garnet laser in 10 stable vitiligo patients with 20 lesions without control group. (Garg et al, 2019) Among 20 lesions, 60% achieved excellent repigmentation even in 8 weeks and 10% of lesions got good response, 20% had moderate response and only 10% showed poor response over 24 weeks of intervention. Even though different mode of PRP preparation in both studies, effectiveness of growth factors on keratinocyte and melanocyte enhanced repigmentation and showed improvement.

Table 3: Methods of PRP preparation and adverse effects

Study, Year	Whole blood (cc)	Anticoagulant/ Activator	PRP preparation	Centrifugation		Protocol	Adverse Effect of PRP
				Soft	Hard		
Combination of PRP with laser and light-based treatment in vitiligo							
(Kadry et al, 2018)	8	Regen Lab Kit	Single	1500 rpm x 5 min		ID q 2 wk, *6Tx (0.1ml per injection,1cm apart)	Pain, PIH
(Abdelghani et al, 2018)	10 - 20	Sodium citrate /Calcium chloride	Double	1500 rpm x 10 min	2000 rpm x 10 min	ID q 3 wk, *4Tx (0.1ml per injection,0.5cm apart)	NA
(Ibrahim et al, 2016)	10-20	Sodium citrate /Calcium chloride (10:1)	Double	3000 rpm x 7min	4000 rpm x 5min	ID q 2 wk, *8Tx (0.1ml per injection, 2cm apart)	Pain
(Khattab et al, 2019)	25	Trisodium citrate	Double	1157 - 1336rpm x 10min	1500-2000 rpm x 15min	ID q 3 wk, *6Tx (0.1ml per injection, 1cm apart)	PIH
Combination therapy of PRP with local and systemic therapy in vitiligo							
(Saify et al, (May. 2019))	NA	India FDA protocol	NA	NA	NA	Local ID/topical or Systemic IV q 30 days, *6T	Erythema
Use of laser with PRP in vitiligo surgery							
(Garg et al, 2019)	10	Citrate dextrose, Y cell bio kit	Single	3200rpm x 4min		1.5ml of thick suspension of PRP with dermoepidermal fragments kept in incubator at 37'C for 1 minute *1T	Pain
(Parambath et al, 2019)	NA	NA	Double	945 rpm x 7 min	2835 rpm x 12 min	Suspending NCES in PRP *1T	Pain

ID= intradermal, PIH = post inflammatory hyperpigmentation, NA = not available, rpm= revolution per minute, NCES = non-cultural epidermal suspension

5. Discussion

Total seven manuscripts met with the study inclusion criteria and were included in this study. In our analysis, 5 randomized comparative study, 1 open prospective study with large sample size and 1 split body double blind randomized study. Only two articles mentioned about the mean disease duration of vitiligo patients. Moreover, only a few studies mentioned with detail method of PRP preparation and sequence of centrifugation. Regards to literature review, Sardana studied overview of medical therapies and phototherapy in vitiligo based on their pathogenesis and analyzed that PRP monotherapy is ineffective in vitiligo but superlative results in combination therapy. Another issue reported about PRP does not help repigmentation in pressure bearing areas or acrofacial area. (Sardana & Verma, 2018).

Based on the evidence based data, many therapeutic approaches have been approved to treat according to vitiligo's complex pathogenesis and a few of them are still challenging. Most modalities are still controversial to regard as the best treatment of choice since they come with different responses as well as require a prolonged course. Regards to the exaggeration of multifactorial and polygenic nature of vitiligo, some facts pave the way to combination therapy in order to get superior response rather than monotherapy. Some existing treatment modalities such as topical and systemic immunomodulators, corticosteroids, topical calcineurin inhibitors, calcipotriol, phototherapy, excimer laser and surgical techniques like cellular or tissue grafting, with or without combination therapy to halt the disease advancement, stabilizing the progressive lesion and reactivate the melanocyte for repigmentation. (Rodrigues, Ezzedine, Hamzavi, Pandya, & Harris, 2017) A novel autologous therapeutic modality, platelet-rich plasma (PRP), has innovated for numerous therapeutic options in dermatology, for instance, alopecia, acne scarring, skin rejuvenation, chronic wounds and vitiligo. The role of platelet-rich plasma in modulating local T cell immunity, growth factors, cytokine and other anti-inflammatory mediators secreted from the alpha and beta granules of platelets which involves in local immunity regulation, preventing the melanocyte damage and effect on melanin synthesis. (Hesseler & Shyam, 2019) PRP therapy with high concentration of trophic factors tends to skin repigmentation in vitiligo by stimulation of proliferation, keratinocyte and fibroblast interaction with melanocytes, adhesion and activation of undifferentiated stem cell. (Carrillo-Mora, Gonzalez-Villalva, Macias-Hernandez, & Villasenor, 2013)

To the best of our knowledge, this study will be the first to evaluate the efficacy of platelet-rich plasma as combination therapy for vitiligo treatment. In this study, homogenous outcome measurements, repigmentation scale and visual analogue scale for investigator's global assessment, were used so it was easily to evaluate the efficacy of platelet-rich plasma as combination therapy compared with control. Based on current study, several clinical trials proved about the efficacy of PRP as combination therapy got superior outcome and highest patients' satisfaction compared to the other groups. Several mechanisms proposed to enhance the repigmentation of vitiligo, PRP is a natural biological product having variety of growth factors which are enhancing the efficacy of repigmentation when PRP combined with standard vitiligo treatment. One synergistic result of PRP combination therapy is the stimulatory effect on melanocyte regeneration by UV radiation and ablative CO2 laser remove the skin barriers so it made better penetration of PRP into the depigmented skin for improving repigmentation.

Nevertheless, large scale clinical measures are still required since exact mechanism of PRP on vitiligo is still unknown. Therefore, combination therapies rather than monotherapy were proved for better repigmentation and outcomes in vitiligo. As an adjunct therapy, use of PRP is significant in both clinically and statistically in repigmentation compared with PRP alone or other control group. Generally, PRP is considered as safe apart from minimal side effects like pain, erythema and minor complications for short duration immediately after procedure.

6. Conclusion

The purpose of this study is to highlight the efficacy of platelet-rich plasma as combination therapy for vitiligo. Since a novel autologous PRP therapy has high concentration of growth factors which tend to skin repigmentation in vitiliginous skin, it can generally regard as safe with efficient. Large population with long duration clinical trials are still necessary to measure the exact efficacy and mechanism of PRP on vitiliginous skin. As a result, PRP was found to be effective as adjunct treatment.

7. Acknowledgement

With deepest gratitude and appreciation, I humbly give thanks to the people who advise and support with their greatest effort and encouragement**.** Among these people, I would like to acknowledge my sincere appreciation to my thesis advisor, my family and colleagues for their kind encouragement throughout my entire work**.** This study will not be accomplished without them**.**

8. References

Abdelghani, R., Ahmed, N. A., & Darwish, H. M. (2018). Combined treatment with fractional carbon dioxide laser, autologous platelet-rich plasma, and narrow band ultraviolet B for vitiligo in different body sites: A prospective, randomized comparative trial. *J Cosmet Dermatol, 17*(3), 365-372. doi:10.1111/jocd.12397

Carrillo-Mora, P., Gonzalez-Villalva, A., Macias-Hernandez, S. I., & Villasenor, C. P. (2013). [Platelets-rich plasma: a versatile tool for regenerative medicine?]. *Cir Cir, 81*(1), 74-82.

Garg, S., Dosapaty, N., & Arora, A. K. (2019). Laser Ablation of the Recipient Area With Platelet-Rich Plasma-Enriched Epidermal Suspension Transplant in Vitiligo Surgery: A Pilot Study. *Dermatol Surg, 45*(1), 83-89. doi:10.1097/dss.0000000000001641

Hesseler, M. J., & Shyam, N. (2019). Platelet-rich plasma and its utility in medical dermatology: A systematic review. *J Am Acad Dermatol, 81*(3), 834-846. doi:10.1016/j.jaad.2019.04.037

Higgins JPT, T. J., Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). (Cochrane, 2019). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). www.training.cochrane.org/handbook.

Ibrahim, Z. A., El-Ashmawy, A. A., El-Tatawy, R. A., & Sallam, F. A. (2016). The effect of platelet-rich plasma on the outcome of short-term narrowband-ultraviolet B phototherapy in the treatment of vitiligo: a pilot study. *J Cosmet Dermatol, 15*(2), 108-116. doi:10.1111/jocd.12194

Kadry, M., Tawfik, A., Abdallah, N., Badawi, A., & Shokeir, H. (2018). Platelet-rich plasma versus combined fractional carbon dioxide laser with platelet-rich plasma in the treatment of vitiligo: a comparative study. *Clin Cosmet Investig Dermatol, 11*, 551-559. doi:10.2147/ccid.S178817

Khattab, F. M., Abdelbary, E., & Fawzi, M. (2019). Evaluation of combined excimer laser and platelet-rich plasma for the treatment of nonsegmental vitiligo: A prospective comparative study. *J Cosmet Dermatol*. doi:10.1111/jocd.13103

Parambath, N., Sharma, V. K., Parihar, A. S., Sahni, K., & Gupta, S. (2019). Use of platelet-rich plasma to suspend noncultured epidermal cell suspension improves repigmentation after autologous transplantation in stable vitiligo: a double-blind randomized controlled trial. *Int J Dermatol, 58*(4), 472-476. doi:10.1111/ijd.14286

Rashighi, M., & Harris, J. E. (2017). Vitiligo Pathogenesis and Emerging Treatments. *Dermatol Clin, 35*(2), 257-265. doi:10.1016/j.det.2016.11.014

Rodrigues, M., Ezzedine, K., Hamzavi, I., Pandya, A. G., & Harris, J. E. (2017). Current and emerging treatments for vitiligo. *J Am Acad Dermatol, 77*(1), 17-29. doi:10.1016/j.jaad.2016.11.010

Saify, K., Gupta, P., & Sharma, D. C. ((May. 2019)). Treatment of Vitiligo by PRP and Umbilical Cord Blood: A prospective study in 120 cases. *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), Volume 18*(Issue 5 Ser. 12, PP 01-05). doi:10.9790/0853-1805120105

Sardana, K., & Verma, G. (2018). Overview of Medical Therapies and Phototherapy in Vitiligo Based on Their Pathogenetic Action and the Role of Platelet-Rich Plasma. *J Cutan Aesthet Surg, 11*(4), 167-168. doi:10.4103/jcas.Jcas_68_17

van Geel, N., Ongenae, K., & Naeyaert, J. M. (2001). Surgical techniques for vitiligo: a review. *Dermatology, 202*(2), 162-166. doi:10.1159/000051626