

Platelet-Rich Plasma in the Treatment of Alopecia Areata: A Review



Hind M. Almohanna¹, Azhar A. Ahmed², Jacob W. Griggs³ and Antonella Tosti³

Platelet-rich plasma (PRP) is an autologous preparation of plasma with concentrated platelets containing various growth factors and cytokines that enhance the body's inherent capacity to repair and regenerate hair follicles. A few studies and case reports support the use of PRP for the treatment of alopecia areata (AA). Further large-scale studies are needed to evaluate the efficacy of PRP as monotherapy or in association with other therapeutic modalities for AA. Although PRP is relatively safe and potentially effective, there is no standardized protocol or recommendations for the number of PRP sessions required to treat and maintain hair growth.

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INTRODUCTION

Alopecia areata (AA) causes nonscarring alopecia through an autoimmune mechanism targeting the hair follicles. The estimated lifetime incidence of AA is around 2%, with no difference in incidence between genders (Fricke and Miteva, 2015; Mirzoyev et al., 2014). AA has an unpredictable course, with 34–50% of patients recovering within 1 year, and 14–25% of patients progressing to alopecia totalis (AT) or alopecia universalis (AU) (Gip et al., 1969; Tosti et al., 2006). Approximately 24.2% of patients with AT and/or AU reported hair regrowth $\geq 90\%$ over 10 years (Jang et al., 2017). Poor prognostic factors include the onset of AA at a younger age, family history of AA, history of atopy, ophiasis type, nail dystrophy, extensive hair loss, or the presence of other autoimmune diseases (Madani and Shapiro, 2000). Treatment of AA is challenging, and hair loss may remit naturally, although spontaneous hair regrowth may take months to years (Pratt et al., 2017). Traditional therapeutic modalities include corticosteroids, immunosuppressants, topical immunotherapy, and light therapy (Pratt et al., 2017; Park et al., 2013). Several new treatments are under investigation, including IL-2 agonist, IL-17 inhibitors, abatacept, Jak

inhibitors, and platelet-rich plasma (PRP) (Darwin et al., 2018). Although an IL-4 receptor antagonist has been reported to induce AA (Flanagan et al., 2019; Mitchell and Levitt, 2018), it also showed efficacy in treating AA (Barroso-García et al., 2018; Darrigade et al., 2018; Penzi et al., 2018).

PRP was introduced to the medical field as a possible hemostatic agent used in surgery and for chronic nonhealing wounds (Cieslik-Bielecka et al., 2012; DelRossi et al., 1990). After that, PRP gained attention in other areas, including plastic surgery, orthopedics, and maxillofacial surgery for its usage in the wound healing process and tissue repair (Albanese et al., 2013). Recently, new indications for PRP have been developed in dermatology, including scar revision, skin rejuvenation, wound healing, and striae distensae (Arshdeep and Kumaran, 2014). Moreover, PRP has been implemented to regrow hairs in treating androgenetic alopecia and AA and to boost graft survival in hair transplantation (Schivone et al., 2014). This review summarizes the efficacy, safety, and mechanism of action of PRP injections in treating AA.

PRP MECHANISM OF ACTION AND PREPARATION

PRP is an emerging technology that uses an autologous preparation of plasma with concentrated platelets to stimulate hair growth. PRP is composed of several growth factors and cytokines that stimulate hair follicle repair and regeneration (Dhillon et al., 2012; Marwah et al., 2014). Recent evidence suggests that PRP may positively impact wound repair, angiogenesis, cellular differentiation, and the proliferation of adipose precursor cells (Marwah et al., 2014). The efficacy of PRP as adjuvant therapy for nonscarring alopecias is supported by the literature (Aasly and Anke, 1989; El Taieb et al., 2017; Trink et al., 2013).

PRP consists of over 20 growth factors secreted by a high concentration of platelets. Hair regrowth is stimulated by these growth factors, which include PGDF, VEGF, TGF, fibroblast growth factor (FGF), connective tissue growth factor, EGF, and IGF-1 (Akiyama et al., 1996). These growth factors bind to the corresponding receptors expressed by stem cells in the hair follicle bulge and surrounding tissues. Ligand binding stimulates the proliferation phase of the hair follicle, giving rise to the anagen follicular unit and promoting hair growth (Akiyama et al., 1996; Gkini et al., 2014). In addition, the growth factors in PRP initiate pathways, which cause angiogenesis and the development of adnexal structures. Anagen-associated angiogenesis has been linked to VEGF secreted by keratinocytes located in the outer root sheath and fibroblasts of the dermal papilla (Cervelli et al., 2014).

Li et al. (2012) demonstrated that in vitro, PRP affects the dermal papilla cells by increasing cell proliferation,

¹Department of Dermatology and Dermatologic Surgery, Prince Sultan Military Medical City, Riyadh, Saudi Arabia; ²Department of Dermatology, King Fahad General Hospital, Medina, Saudi Arabia; and ³Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, University of Miami Hospital, Miami, Florida, USA

Correspondence: Hind M. Almohanna, Department of Dermatology and Cutaneous Surgery, University of Miami Hospital, 1295 NW. 14th Street, South Building, Suite L, Miami, Florida 33125, USA. E-mail: mohannahind@gmail.com

Abbreviations: AA, alopecia areata; AT, alopecia totalis; AU, alopecia universalis; FGF, fibroblast growth factor; PRP, platelet-rich plasma; TAC, triamcinolone acetonide

increasing the phosphorylation of extracellular signal-regulated kinases and Akt, increasing *Bcl-2* expression, increasing β -catenin activity, and increasing *FGF-7* expression. The activation of extracellular signal-regulated kinases is associated with promoting cell growth, whereas Akt activation promotes cell survival and inhibits apoptosis. In addition, *Bcl-2* is involved in the inhibition of apoptosis (Schenk et al., 2017). β -catenin has an important role in the formation of hair placodes and the differentiation of stem cells into hair follicle cells (Sohn et al., 2009), supporting the theory that PRP contributes to hair growth by inducing the differentiation of stem cells to hair follicle cells. β -catenin is also involved in signaling for melanocyte differentiation (Luciani et al., 2011). *FGF-7* contributes to hair growth by prolonging the anagen phase and delaying entry to the catagen phase (Danilenko et al., 1995). Related to *FGF-7*, basic FGF (also called *FGF-2*) is present in PRP (Krüger et al., 2013); basic FGF promotes melanin synthesis by melanocytes (Puri et al., 1996). The effects of β -catenin and basic FGF on melanocyte differentiation and melanin synthesis may contribute to the ability of PRP to promote the growth of pigmented hairs in AA. Ki-67, a marker of cellular proliferation, is present in significantly higher levels in hair taken from patients treated with PRP (Trink et al., 2013).

PRP may also be effective in AA through anti-inflammatory mechanisms owing to its ability to suppress MCP-1, and owing to the presence of TGF β (β 1 and β 2) (Amable et al., 2013; El-Sharkawy et al., 2007). MCP-1 is a chemotactic cytokine involved in monocyte and T lymphocyte recruitment (Noris et al., 1995). Moderate expression of MCP-1 in the hair bulb is associated with AA, which is hypothesized to play a role in the pathogenesis of AA by recruiting T lymphocytes and monocytes to the hair bulb, resulting in a local inflammatory reaction around the hair bulb (Benoit et al., 2003). TGF β is a known immune modulator, which inhibits T lymphocyte proliferation (Kehrl et al., 1986). Levels of TGF β 1 in the serum were found to be significantly reduced in patients with AA (Tembhre and Sharma, 2013). The hair follicle locally produces TGF β 1, whose immunosuppressant action acts with other mechanisms to create a local "immune privileged" environment, the disruption of which is hypothesized to contribute to the pathogenesis of AA (Paus et al., 2003).

No consensus exists for the standardized protocol of the PRP preparation and procedure. Many techniques have been described, and several PRP systems are commercially marketed. Currently, there is no evidence-based information comparing the protocol of administration, the frequency of injections, or the number of treatment sessions (Maria-Angeliki et al., 2015). Generally, 8–60 ml of fresh venous blood is collected from an individual subject, and the blood sample undergoes centrifugation. The centrifuge separates the red blood cells from lighter plasma with a buffy coat at the interface. After that, the plasma and buffy coat are aspirated (Lynch and Bashir, 2016). Protocols yield an increase in the concentration of platelet ranging from three to 8-fold (Trink et al., 2013; Eppley et al., 2004). A review of the literature has revealed that seven studies showed preliminary evidence for the potential effect of PRP in treating AA.

PRP IN THE TREATMENT OF AA

Overview

El Taieb et al. (2017) and Trink et al. (2013) conducted high quality randomized, placebo-controlled trials that showed significant improvement of AA after PRP treatment compared with placebo, providing particularly strong evidence of the efficacy of PRP in the treatment of AA. Two nonrandomized trials showed improvement in hair regrowth with PRP treatment (Shumez et al., 2015; Singh, 2015). In addition, two case reports support the efficacy of PRP (Donovan, 2015; Mubki, 2016). A case series showed some improvement in regrowth with PRP treatment, though regrowth was not maintained at further follow-up (d'Ovidio and Roberto 2014).

Randomized, Placebo-controlled clinical trials

Trink et al. (2013) conducted a randomized, double-blind, placebo-, and active-controlled, half-head parallel-group study to evaluate the efficacy and safety of PRP on AA. A total of 45 subjects were randomized to one of three groups: PRP, triamcinolone acetonide (TAC, 2.5 mg/cm³), or placebo. Three treatments with a 1-month interval were administered. All subjects were evaluated at baseline, 2 months, 6 months, and 12 months. The results of the study revealed that intralesional TAC and PRP resulted in significant hair regrowth in AA lesions compared with placebo or to baseline. Results were sustained at a 1-year follow-up. PRP and TAC decreased the number of dystrophic hairs as evaluated by dermoscopic findings and also minimized the itching or burning sensation of treatment. Nonetheless, PRP revealed significantly better dermoscopy results than having intralesional TAC. This study supports the use of PRP in AA to stimulate hair regrowth, especially of pigmented hairs, with a lower chance of relapse. Of note, the method of centrifugation that has been used in this study produced a platelet count that was, on average, 3.5 times higher than whole blood. No adverse effects were noted with PRP, TAC, or placebo administration (Trink et al., 2013).

El Taieb et al. (2017) conducted a randomized controlled study to investigate the efficacy of PRP in treating AA. A total of 90 patients with patchy AA and/or AT and/or AU were included with ages between 10 and 40 years, with no therapy for at least 3 months before the study. Patients were randomized into three groups, each of which included 30 patients. The first group was treated with topical minoxidil 5% twice daily (six pubs per time) as a monotherapy. The second group was treated with three PRP treatment sessions every 4 weeks. The third group received topical panthenol cream twice daily as a placebo. Digital photography and dermoscopic examination were done before treatment and monthly after treatment for 3 months. For PRP preparation, 10 ml of blood was drawn from each patient and placed in two test tubes as 5 ml each. The collected blood was centrifuged at 3,000 r.p.m. for 10 minutes, and blood was separated into an inferior red phase and superior plasma supernatant phase. The PRP fraction was separated and suspended with calcium gluconate. The total volume of collected PRP was about 4 ml. Significant hair regrowth was noticed in patchy AA (70%) and AU (30%) after three sessions of PRP; however, AT did not respond to PRP. PRP led to significant, fully pigmented hair growth in AA lesions. Short vellus hair and yellow dots were

significantly decreased after PRP treatment. Minoxidil group showed improvement of patchy AA (81%) more than AT and/or AU. Only 30% of patients in the control group experienced a significant hair growth of patchy AA type. Although both PRP and minoxidil 5% showed a significant increase in hair growth, subjects treated with PRP exhibited a significant decrease in short vellus hair, unlike patients treated with minoxidil and control who showed a significant increase in short vellus hair. Participants who underwent PRP treatments had better and an earlier response than participants treated with minoxidil 5% in terms of hair regrowth, reduction of short vellus hair, broken hairs, and yellow dots (El Taieb et al., 2017).

Nonrandomized clinical trials

Shumez et al. (2015) conducted a nonrandomized controlled study on 74 patients with AA (excluding AA with more than 25% involvement). Subjects were divided into two groups; the first group involved 48 participants who received TAC 10 mg/ml, and the second group included 26 patients that underwent PRP injections. PRP was prepared with a double centrifugation technique, where 20 ml of whole blood was drawn and centrifugated at 5,000 r.p.m. for 15 minutes. PRP was separated, and the residual plasma above the buffy coat was centrifugated again at 2,000 r.p.m. for 5–10 minutes. This soft spin collects the residual PRP. Calcium chloride (10%) was added as an activator (0.3 ml for 1 ml PRP). Three sessions were performed to each patient at 3-week intervals. Patients were evaluated at 3 months by “assessment of overall improvement” scale, serial photographs, and dermoscopic examination. The results showed a remission rate of 52.8% and 35.4% in PRP and TAC, respectively, at week 6. However, this difference was statistically insignificant ($P = 0.597$). The overall improvement at week 9 and week 12 showed complete hair regrowth of all patients in both groups (Shumez et al., 2015).

A prospective study was carried out to evaluate the efficacy of PRP in AA. A total of 20 patients with AA were enrolled in this study. A total of 25 ml of peripheral blood was drawn, then PRP was separated and injected in the subfollicular plane. All patients received six sessions at 4-week intervals. The subjects were evaluated at 6 months and 1 year. The results revealed that good hair regrowth was noticed by most of the participants except for one patient who had a relapse and minimal hair regrowth. None of the patients developed serious side effects (Singh, 2015).

Case reports and/or series

Donovan (2015) reported a case of a 41-year-old woman with AA (ophiasis type) for 2 years that had failed intralesional TAC. Treatment was performed with autologous PRP (anthrax angel system) after drawing 120 ml from the patient's blood and processing it according to the manufacturer's instructions. PRP was mixed with platelet-poor plasma to achieve a final platelet concentration of 3.5 times above baseline. A total of 9 ml of PRP was injected into the patient's occipital area. Mild tenderness was controlled with acetaminophen on the procedure day and the following 2 days. The patient experienced that hair regrowth started 1 month after the procedure with minimal side effects (Donovan, 2015).

Another case report supports the positive effect of PRP, where Mubki (2016) used a combination of PRP and intralesional TAC on half of the scalp of a patient with long-standing AA and intralesional TAC alone in the other half of the scalp. The right side of the scalp was treated with both intralesional TAC (2.5 mg/ml a total of 4 ml) and intradermal injections of PRP (2–3 ml), and the left half of the scalp was treated with intralesional TAC only (2.5 mg/ml a total of 4 ml). Eight sessions were performed on the right scalp over 16 weeks (four sets of PRP alternating with four sessions of intralesional TAC at 2 weeks interval), whereas four treatment sessions were performed on the left side of the scalp with intralesional TAC only. Regarding the PRP preparation, 18 ml of whole blood was drawn from the patient in vacutainers (Pure PRP System, Seoul, Korea) containing ACD-A (trisodium citrate, citric acid, and dextrose). The tube was centrifuged at 1,500 g for 4 minutes. The PRP fraction was separated and suspended with calcium chloride. Assessment of hair regrowth was carried out by using global photography and digital trichoscopy. Two square areas were anatomically marked, each measuring 1 cm × 1 cm over both right and left parietal scalp located at the midpupillary line, 10 cm proximal to the corresponding eyebrow. The patient's response was assessed at baseline and 2 weeks after the last treatment. Both treatment modalities showed an increase in terminal hair number (16% for PRP and TAC combination vs. 12% for TAC alone). There was an increase in mean hair shaft diameter (+35%) with combination therapy and a decline (–4%) with TAC monotherapy. (Mubki, 2016).

In Contrast, d'Ovidio and Roberto (2014) reported a case series of nine patients with chronic AA (> 50 of the scalp involved) who received PRP. The patients underwent three treatment sessions with a 45–60 days interval. The protocol for PRP preparation was similar to the study of Trink et al. (2013). The platelet concentration was about 3–4 times higher than the quantity found in the blood. A total of 2–4 ml PRP was injected intradermally. The patients were evaluated at baseline, 8 months, and 1 year. In the eighth month, six subjects had obtained regrowth of terminal pigmented hair, and the others noted nonpigmented vellus hairs in the seats of infiltration after the second session of PRP infusion. At an average follow-up of 1 year, none of the patients still had the hair regrown (d'Ovidio and Roberto, 2014).

Adverse effects

The PRP procedure is a relatively effective and safe intervention with minimal adverse effects, including temporary and tolerable pain during treatment, mild headache which may regress with acetaminophen, minimal itching, transient erythema and edema, and desquamation (Alves and Grimalt, 2016; Anitua et al., 2017; Gentile et al., 2015; Gkini et al., 2014; Kachhawa et al., 2017; Kang et al., 2014; Khatu et al., 2014; Singhal et al., 2015). An unpublished anecdotal report of three patients who developed telogen effluvium with psoriasiform scalp dermatitis 2–6 weeks after being treated with PRP was seen by Dr Tosti (de Sousa and Tosti, 2013). To date, there are no reports of infections, folliculitis, panniculitis, hematoma, or seroma formation (Badran and Sand, 2018). Patients who received PRP in the

Trink et al. (2013) study demonstrated the reduction of burning and itching compared with baseline. Contraindications to PRP procedure include platelet dysfunction, thrombocytopenia, coagulation disorders, anticoagulant therapy, hepatitis, hemodynamic instability, local infection at the site of blood harvest or PRP injection, and patients who are prone to keloid formation (Badran and Sand, 2018).

CONCLUSION

There is initial supporting evidence to use PRP for the treatment of AA; however, the lack of standardized protocol precludes any recommendations for the number of PRP sessions required to treat AA. PRP is relatively safe and potentially effective for the regrowth of pigmented hairs in AA. Further large-scale studies are needed to evaluate the efficacy of the PRP procedure as monotherapy and whether it is superior over current therapeutic modalities for AA.

ORCIDs

Hind M. Almohanna: <http://orcid.org/0000-0003-3026-5512>

Azhar A. Ahmed: <http://orcid.org/0000-0002-5030-7110>

Jacob W. Griggs: <http://orcid.org/0000-0003-0263-0228>

Antonella Tosti: <http://orcid.org/0000-0001-5516-4043>

CONFLICT OF INTEREST

AT is a consultant for P&G, DS Laboratories, Monat, Pfizer, Thirty Madison, and Almirall, Principal Investigator for Incyte, Pfizer, Aclaris, Eli Lilly, and Nutrifol and serves on the advisory board of Leo Pharma. HMA, AAA, and JWG state no conflict of interest.

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