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Treatment Options for Primary Cicatricial Alopecia: Established Therapies and New Concepts

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Abstract

The incidence of primary cicatricial alopecias (PCAs) have risen dramatically in recent decades, however effective treatments for PCAs have lagged. Current treatment options vary widely in their efficacy, and no treatments are able to stimulate hair regrowth in the scarred lesions of PCAs. With increasing knowledge of the pathogenesis of scarring alopecia, new targets for treatment are emerging. This mini-review aims to succinctly summarize the established treatment options as well as the newer investigative therapies and novel targets in the treatment of scarring alopecia. Some of the newer treatment options include JAK inhibitors, naltrexone, photodynamic therapy with superluminescent diodes, platelet-rich plasma, oral fusidic acid, retinoids, thiazolidinediones and TNF-alpha inhibitors. There are also options for surgical hair restoration in patients with controlled, stable disease.

Keywords: Folliculitis; Immunosuppressants; Cicatricial alopecia; scarring alopecia

Abbreviations: PCA: Primary Cicatricial Alopecias; HF: Hair Follicle; LPP: Lichen Planopilaris; FFA: Frontal Fibrosing Alopecia; CCCA: Central Centrifugal Cicatricial Alopecia; PRP: Promoting Properties of Platelet-Rich Plasma; FUT: Follicular Unit Transplantation.

Introduction

The efficacy of available treatment options for primary cicatricial alopecia (PCA) is highly variable. With no large-scale, double-blinded, randomized control trials, treatment options for PCA have been based predominantly on generally-accepted guidelines and case series. Further complicating the search for effective treatments is the unpredictable clinical course of scarring alopecia, which is variable in both severity and duration. Since no treatments at this time are able to stimulate hair regrowth in regions of scarring, current options are aimed at controlling active disease and preventing disease progression.

Background

One of the main drivers in the pathogenesis of PCA is postulated to be the infiltration of the hair follicle (HF) by inflammatory cells. The region of the hair follicle that is attacked is the isthmus, which is adjacent to where the

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epithelial hair follicle stem cells, located within the bulge, reside. This attack results in loss of the HF stem cells and eventual fibrosis of the follicle, leading to permanent, irreversible alopecia. This review will focus on primary cicatricial alopecia, which can be further subdivided based on the specific type of inflammatory infiltrate found around the hair follicle – lymphocytic, neutrophilic and mixed type. Lymphocytic PCAs include lichen planopilaris (LPP), frontal fibrosing alopecia (FFA), central centrifugal cicatricial alopecia (CCCA), pseudopelade of Brocq, discoid lupus and Graham-Little syndrome. Neutrophilic PCAs include folliculitis decalvans, tufted folliculitis and dissecting cellulitis. Mixed type PCAs are folliculitis keloidalis, folliculitis necrotica and erosive pustular dermatosis.

As a general overview, treatment for neutrophilic type PCAs, such as folliculitis decalvans and dissecting cellulitis, tends to focus on antibiotics and isotretinoin (respectively), while the mainstays for treatment of lymphocytic types of PCA have been combination therapy with corticosteroids, immunosuppressants and systemic anti-inflammatories. Therapies for the subcategory of mixed type cicatrical alopecia include the usual anti-inflammatories and antimicrobials. Clinicians often add topical minoxidil to the treatment regimen in an effort to stimulate hair growth from remaining unscarred hair follicles.

Methods

A literature search was conducted using the US National Library of Medicine National Institute of Health PubMed database in September of 2019. A total of 104 articles were reviewed, consisting of case studies, reviews, retrospective studies, small open-label trials and primary studies. Of the reviewed literature, 27 articles were classified as reviews, 39 as research and 38 as cases. No large-scale, double-blinded, randomized control trials were found. Publications originally in English and those with an English translation were included. MeSH terms used in the literature search included primary cicatricial alopecia, cicatricial alopecia, scarring alopecia, lichen planopilaris, frontal fibrosing alopecia, central centrifugal cicatricial alopecia, novel and treatment.

Established, consensus treatment options

Treatment of PCAs has been historically difficult. Evidence for the current treatment options comes from consensus guidelines and retrospective studies, case reports and case series. Additionally, assessment of treatment responses is not standardized, and there are varying methods used across the existing publications. The following medications have been used with varying degrees of success in primary cicatricial alopecia, and all are widely regarded as acceptable options for treatment.

Corticosteroids

Corticosteroids have long been a mainstay in the treatment of PCA. They are used as topical treatment, intralesional injections, and systemic therapy. Topical steroids vary largely by strength, potency, and formulation. Intralesional injection is usually triamcinolone. A typical choice for systemic use is prednisone or prednisolone. For lymphocytic PCAs, specifically lichen planopilaris (LPP), first line therapy is generally recognized as topical and intralesional corticosteroids.

Antibiotics

Tetracyclines

The tetracyclines, specifically minocycline and doxycycline, have anti-inflammatory properties which make them useful in treating PCA.

Non-tetracyclines

The non-tetracycline antibiotics – such as rifampicin, clindamycin, cephalosporins, ciprofloxacin, SMX-TMP and erythromycin – are a treatment staple of neutrophilic PCA.

Topical antibiotics

Antibiotics with a topical formulation include clindamycin, erythromycin and mupirocin. They are used mostly for neutrophilic PCA. When used in combination with topical corticosteroids and oral antibiotics, topical antibiotics are the most effective treatment for neutrophilic cicatricial alopecia [1].

Antimalarials

Hydroxychloroquine is an antibiotic derived from quinine and was originally used to treat malaria. It came into favor as a treatment for PCA in the mid 2000's because of its anti-inflammatory properties. Response rates in PCA are variable and caution must be exercised when using this drug as it is known to cause dose-dependent retinal toxicity.

Immunomodulators

Systemic immunomodulators

Immunosuppressants such as cyclosporine, methotrexate, mycophenolate mofetil seem to be one of the more

effective classes of PCA treatments [2]. One of the few randomized control trials (n=29) in the literature shows that methotrexate is more effective than hydroxychloroquine in patients with classic refractory LPP, as measured by decreased disease activity index (LPPAI) and reported alleviation of symptoms [3]. Additionally, a recent retrospective review looked at efficacy of the most widely accepted treatments in LPP and found methotrexate to be the most effective as a monotherapy, with a response rate as high as 87.5% [4].

Topical immunomodulators

Calcineurin inhibitors include tacrolimus and pimecrolimus. These drugs are typically used as adjunctive therapy since tacrolimus has been reported to have relatively poor efficacy as monotherapy, which is likely due to low penetration of the topical formulation [4-6].

Hormonal modulators

Frontal fibrosing alopecia (FFA), a subtype of lymphocytic PCA, is seen mostly in postmenopausal women and is postulated to be hormonally-driven, at least in part [7]. As such, it is not surprising that 5-alpha reductase inhibitors, such as finasteride and dutasteride, are often used to treat FFA. These drugs seem to be the most effective treatment for FFA, despite their limited efficacy in female androgenetic alopecia [8,9].

Narrow band UV light

UV light, specifically 308 nm wavelength ultraviolet-B light delivered via an excimer laser, has been shown to decrease signs of inflammation in LPP patients [10,11], and is usually used as an adjunct therapy.

New concepts and novel treatment targets

The new concepts in PCA treatment include drugs, light devices, autologous biological therapy (such as PRP), and surgical innovations. In recent years, certain cell populations have been implicated in the pathogenesis of PCA that make up the inflammatory milieu surrounding affected hair follicles. This knowledge on the molecular and cellular level is important because it informs potential targets for therapy. The following targets are the result of recent research elucidating the specific inflammatory and pathogenetic pathways of PCAs.

Janus kinase inhibitors

Upregulation of interferon and Janus Kinase signaling pathways is thought to be a critical step in the pathogenesis of LPP [12,13]; therefore we theorized that JAK inhibitors, such as the pan-JAK inhibitor tofacitinib, may successfully attenuate active disease and halt progression. We recently tested this concept in a pilot study of 10 patients with LPP, eight of which experienced clinical improvement and decreased LPPAI scores [14].

Naltrexone

Naltrexone, an opioid antagonist that boasts anti-inflammatory properties [15], is currently being used in the treatment of a range of cutaneous disorders and autoimmune diseases [16]. In these applications, naltrexone is typically given at a low dose (<5 mg). The disease-modulating effects of low-dose naltrexone are thought to occur by increasing anti-inflammatory endogenous opioids like beta-endorphins [17,18], blocking tumor necrosis factor-alpha [19], and enhancing the phagocytic function of macrophages [20]. Naltrexone may be especially beneficial in conditions that affect stem cells, like PCA, since there are opioid receptors on stem cells in the skin [21,22]. A recent case series details four patients who were given low dose naltrexone daily as adjunct therapy for LPP. All patients saw improvement of symptoms and/or reduction of clinical evidence of disease after adding the naltrexone [23]. There may also be utility for topical naltrexone in the setting of PCA for the purpose of symptom control, as 1% naltrexone cream has been effective in alleviating pruritus [24].

Oral fusidic acid

While the use of topical fusidic acid is widely accepted as part of a treatment regimen for folliculitis decalvans, recently fusidic acid was used as mono-oral therapy in a folliculitis decalvans patient (who was also given topical betamethasone, salicylic acid and azelaic acid) with clinical improvement and hair regrowth around the periphery of lesional sites [25].

Retinoids

Oral retinoids have successfully treated lichen planus [26,27], and therefore it is a logical extension for oral retinoids to be used successfully in FFA and LPP [28-30], since they may be part of the disease spectrum of lichen planus. An uncommon variant of LPP that includes involvement of the face (~20% of LPP patients have facial lesions [31]), has also been treated with isotretinoin [32]. Mechanistically, retinoids may be effective in PCA both due to their anti-inflammatory properties as well as their role as PPAR-gamma agonists [33]. While retinoids can be effective, they can also cause hair shedding via telogen effluvium, which is understandably concerning for hair

loss patients [34]. The risk of shedding is highest with the oral retinoid acitretin.

PPAR-ɣ agonists, thiazolidinediones

Early gene expression studies in LPP patients demonstrated evidence of decreased PPAR-ɣ pathway signaling, leading to altered lipid metabolism and aberrant function of sebaceous glands. Since the first case report in 2009, there have been numerous follow up trials demonstrating that LPP responds to the thiazolidinedione, pioglitazone, with up to 72% of patients seeing marked improvement and some patients experiencing complete remission [35-39]. The effects of pioglitazone are dose-dependent, as are its side effects, which increase as cumulative dose increases.

TNF-alpha inhibitors

Tumor necrosis factor-alpha inhibitors have proven useful in the neutrophilic PCA folliculitis decalavans. Infliximab has been used successfully in refractory disease without evidence of recurrence even at one year follow up [40]. Adalimumab has also been successful in inducing remission in folliculitis decalvans that had not responded to any previous therapy. While the most success for TNF-alpha inhibitors has been in treating folliculitis decalvans, there is also one report of a patient with LPP who experienced reduction in disease activity after being treated with adalimumab [41].

Superluminescent diodes (sLED)

A type of photobiomodulation therapy utilizing light-emitting diodes, called superluminescent diodes, was recently evaluated as an adjuvant therapy in patients with scarring alopecia [42,43]. Patients reported decreased symptoms such as itching and burning, reduction of LPPAI and FFASS disease scoring indices, and decreased inflammation coupled with increased number of thick hairs on trichoscopic exam.

Platelet-rich plasma

Due to the theoretical anti-inflammatory and growth-promoting properties of platelet-rich plasma (PRP), it is a popular but controversial topic in many areas of medicine, including hair loss. Most of the literature focuses on PRP in androgenetic alopecia, but there are a small number of cases reported outlining the use of PRP in the setting of PCA. Platelet-rich plasma administration has been successfully used as adjunct treatment in LPP, CCCA and FFA [44-47]. A recent case report demonstrates the efficacy of PRP as an adjunct therapy in refractory FFA of not only the hairline, but the eyebrows as well [47]. Although the evaluation of PRP in PCAs is preliminary, the few cases that are reported in the literature are promising.

Avoidance of triggers

Investigation into potential triggers for FFA has increased in recent years as incidence of FFA is rising. In 2016, Aldoori et al first suggested a potential link between the ingredients in facial skin care products/sunscreens and FFA, and there have since been multiple corroborating publications [48-51]. Further support for this idea includes a report of hair regrowth after discontinuation of sunscreen on the forehead in a patient previously diagnosed with FFA, and a report of LPP arising in a patient's part line, an area of long term daily spray sunscreen application [52,53].

Patch testing conducted so far has found that around 50% of FFA patients have a positive reaction to fragrances used in skin care products, but there have been no reports of positive reactions to sunscreen-specific allergens [51,54]. It should be noted that in the general population allergy to sunscreen is very rare, with patch testing suggesting an incidence of only 0.9% [55]. Taken together, the collective data does suggest a potential association with ingredients in personal products, raising the possibility of an allergic mechanism as part of the disease process in FFA. Therefore, future utilization of specific patch testing will likely help elucidate if facial skin care products, including sunscreens, are associated with the development of FFA.

Treatment of permanent hair loss in inactive disease

At present, the most common surgical options for hair loss are follicular unit transplantation (FUT) and scalp reduction. Newer surgical options such as artificial hair implantation, which utilizes a polyamide fiber to simulate a human hair, show encouraging results with low complication rates and high patient satisfaction scores [56]. Before any surgical procedures or hair transplantation are contemplated in PCA patients, it is important that all inflammatory activity has ceased in order to maximize the chances of satisfactory outcomes. Disease should be stable and inactive for 1-2 years before attempting transplantation [57]. Some subtypes of primary cicatricial alopecia, such as CCCA, discoid lupus erythematous, and pseudopelade Brocq, may be more amenable to traditional hair transplant surgery, while LPP and FFA seem to have more mixed results after surgery [58]. A new and promising therapy on the horizon to address permanent hair loss involves regrowing hair follicles through tissue engineering and cell therapy [59-

61]. Recent laboratory data from our group and others suggest it may be possible to gain new, functional hair follicles by introducing vascularized human skin constructs with potential to grow new hair follicles in bald/scarred scalp skin [62], which could open new treatment approaches in PCA.

Conclusion

There are many options when it comes to treating scarring alopecia, albeit with variable degrees of success. Some are more general in their targets (corticosteroids) whereas some newer options target very specific enzymes or inflammatory pathways (JAK, TNF-alpha, PPAR-gamma). At this point, aggressive combination therapy is the most effective approach, but evidence for efficacy of current options is sparse and comes mainly from small case series or case studies. Consequently, there is a need for double-blinded, randomized controlled trials with a large number of subjects to elucidate a gold standard. Regardless of choice of therapeutic agents, patience and patient adherence are important in achieving results, as the mean time to remission can be up to two years [62], and even then disease recurrence and flares are common.

New and targeted therapeutic approaches based on emerging research are being explored and there is great potential for breakthrough treatments. Some of these new and exciting targets of treatment include JAK inhibitors, naltrexone, superluminescent diodes, PRP and oral fusidic acid, to name a few. Future directions may focus on patch testing to determine if there is a link between facial skin care products and an allergic mechanism involved in the development of PCA. In the future, harnessing the potential of cell therapy and tissue engineering may offer new approaches to permanently restore hair follicles in PCAs.

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