

# Alopecia areata: a new treatment plan

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**Abstract:** Many therapeutic modalities have been used to treat alopecia areata, with variable efficacy and safety profiles. Unfortunately, none of these agents is curative or preventive. Also, many of these therapeutic agents have not been subjected to randomized, controlled trials, and, except for topical immunotherapy, there are few published studies on long-term outcomes. The treatment plan is designed according to the patient's age and extent of disease. In this paper, the therapeutic agents are organized according to their efficacy and safety profiles into first-line, second-line, and third-line options.

**Keywords:** alopecia areata, corticosteroids, immunotherapy, intralesional, phototherapy, sulfasalazine

## Introduction

Alopecia areata is a common, nonscarring, autoimmune disease that can affect any hair-bearing area. Alopecia areata is a lymphocyte cell-mediated inflammatory type of hair loss, but its pathogenesis is not fully understood. The disease can present as a single, well demarcated patch of hair loss, multiple patches, or extensive hair loss in a form of total loss of scalp hair (alopecia totalis) or loss of entire scalp and body hair (alopecia universalis). A number of treatments can induce hair regrowth in alopecia areata but do not change the course of the disease. Treatment is more effective in patchy alopecia areata than in alopecia totalis/alopecia universalis. Therapy for alopecia areata should be tailored in light of severity of the condition and the patient's age. This review discusses the therapeutic options and management strategies for alopecia areata.

## First-line therapies

### Intralesional corticosteroids

Several studies have shown the efficacy of intralesional corticosteroid injections. Abell and Munro reported hair regrowth in 71% of patients with subtotal alopecia areata treated by triamcinolone acetonide injections and in 7% of a placebo group.<sup>1</sup> For limited scalp alopecia areata, intralesional corticosteroid therapy is considered as the drug of choice by many experts. The most widely used agent is triamcinolone acetonide. Different concentrations of triamcinolone acetonide are used, in the range of 2.5–10 mg/mL, but 5 mg/mL is the preferred concentration for the scalp and face. A maximum volume of 3 mL on the scalp in one visit is recommended. Corticosteroid is injected into the deep dermis level or just beneath the dermis in the upper subcutis. The injections can be repeated at 4–6 weekly intervals. The use

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of mesotherapy multi-injectors with 5–7 needles is an alternative approach to decrease injection pain and to make the procedure more homogenous.<sup>2</sup> Side effects include skin atrophy and telangiectasia which can be minimized by the use of smaller volumes and avoiding superficial injections. To alleviate injection pain, topical anesthetic may be applied 30–60 minutes before the treatment. Although the effect of a single intralesional corticosteroid injection has been observed to persist for up to 9 months,<sup>3</sup> reported relapse rates were 29% in limited alopecia areata and 72% in alopecia totalis during a 3-month follow-up period.<sup>1</sup>

## Topical corticosteroids

Many forms of topical corticosteroids have been prescribed for alopecia areata, including creams, gels, ointments, lotions, and foams. Sixty-one percent of patients using 0.1% betamethasone valerate foam achieved more than 75% hair regrowth in comparison with 27% in the 0.05% betamethasone dipropionate lotion group.<sup>4</sup> Topical corticosteroids are far less effective in alopecia totalis and alopecia universalis.<sup>5</sup> A highly potent topical corticosteroid under occlusion is the preferred method when using topical corticosteroids. Folliculitis is a common side effect to topical corticosteroids. Telangiectasia and atrophy may develop rarely. The reported relapse rate is 37%–63%.<sup>5,6</sup>

## Minoxidil

In a placebo-controlled, double-blind study, hair regrowth was observed in 63.6% and 35.7% of the minoxidil-treated and placebo groups, respectively.<sup>7</sup> However, only 27% of the minoxidil-treated patients showed cosmetically acceptable hair regrowth. In another study, hair regrowth was achieved in 38% and 81% of patients treated with 1% and 5% topical minoxidil, respectively.<sup>8</sup> Most studies have shown no beneficial effect of topical minoxidil in alopecia totalis and alopecia universalis.<sup>9</sup> Minoxidil 5% solution or foam is frequently used with other therapeutic agents as an adjuvant therapy. The adverse effects of topical minoxidil include contact dermatitis and facial hypertrichosis.

## Anthralin

A few controlled trials have assessed the efficacy of topical anthralin in the treatment of alopecia areata. In an open study, a cosmetic response was seen in 25% of patients with severe alopecia areata treated using 0.5%–1.0% anthralin cream.<sup>10</sup> In another trial, combination therapy of 5% minoxidil and 0.5% anthralin was used to treat 51 patients with severe alopecia areata; only 11% of patients achieved cosmetically

acceptable hair regrowth.<sup>11</sup> Anthralin needs to be applied in a high enough concentration (0.5%–1%) and sufficiently frequently (daily) to produce a mild irritant reaction in order to be effective. Severe irritation and staining of skin and clothes are some of the possible adverse events with anthralin.

## Topical immunotherapy

Topical sensitizers that have been used in the treatment of alopecia areata include diphenylcyclopropenone, squaric acid dibutylester (SADBE), and dinitrochlorobenzene. Dinitrochlorobenzene is no longer used because it was shown to be mutagenic in the Ames test.<sup>12</sup> Diphenylcyclopropenone is the topical sensitizer of choice. SADBE is expensive and not stable in acetone.<sup>13</sup> Diphenylcyclopropenone is light-sensitive and should be protected from light.<sup>14</sup>

Initially the patient is sensitized using a 2% solution of diphenylcyclopropenone applied to a 4 × 4 cm area of the scalp. After two weeks, 0.001% diphenylcyclopropenone solution is applied to the same half of the scalp. The diphenylcyclopropenone concentration is increased gradually every week until mild dermatitis is observed.<sup>15</sup> The solution should be on the scalp for 48 hours. The scalp should be protected from the sun during this time. Once hair regrowth is obtained on the treated half of the scalp, both sides are treated. Both sides of the scalp can be treated from the start also. Diphenylcyclopropenone is applied on a weekly basis by a trained nurse. If there is no response after 6 months of treatment, diphenylcyclopropenone can be discontinued. SADBE may be tried in poor responders to diphenylcyclopropenone or in those who do not develop a sensitization to 2% diphenylcyclopropenone. SADBE is applied once or twice per week.<sup>16,17</sup> The adverse effects to topical sensitizers include cervical lymphadenopathy, a severe eczematous reaction, urticaria, and postinflammatory pigment changes.<sup>18,19</sup>

The response rate of alopecia totalis/alopecia universalis patients to diphenylcyclopropenone was 17.4% in the largest reported diphenylcyclopropenone study, whereas the cumulative patient response was 77%.<sup>20</sup> Several negative prognostic factors in the treatment of alopecia areata with diphenylcyclopropenone have been suggested, including long duration of disease, alopecia totalis/alopecia universalis, nail changes, atopy, and family history of alopecia areata.<sup>20–22</sup> Recurrence of alopecia areata after achieving significant hair regrowth developed in 62.6% of patients.<sup>20</sup> In a retrospective study of 121 patients with extensive alopecia areata, fexofenadine hydrochloride has been shown to enhance the efficacy of topical immunotherapy.<sup>23</sup>

The mechanism of action of topical sensitizers could be due to perifollicular lymphocyte apoptosis,<sup>24</sup> changes in the peribulbar CD4/CD8 lymphocyte ratio,<sup>25,26</sup> and antigenic competition.<sup>27</sup>

## Prostaglandin analogs

Eyelash hypertrichosis is a common adverse effect to the use of these antiglaucoma eye drops.<sup>28–30</sup> Some case series did not show an effect in the treatment of eyelashes in patients with alopecia areata.<sup>31,32</sup> In a nonrandomized, controlled study of latanoprost (a prostaglandin F2 $\alpha$  analog) eye drops in patients with alopecia universalis, acceptable results (total and moderate hair regrowth) were achieved in 45% of patients.<sup>33</sup> In another retrospective trial, 0.03% bimatoprost eye drops were used once a day for one year. Complete regrowth of the eyelashes was noted in 24.3% of patients and moderate growth in 18.9% of treated subjects.<sup>34</sup> Relapses were observed in 17.5% of the patients, mainly in the slight response group.<sup>33</sup>

## Topical retinoids

In a comparative study of topical tretinoin 0.05%, topical betamethasone dipropionate lotion, and dithranol paste 0.25%, a good response has been seen in 55% of patients treated with topical tretinoin in comparison with 70% and 35% in the topical steroid and dithranol groups, respectively.<sup>35</sup> Although the mechanism for its action in alopecia areata is not completely understood, the associated tretinoin-induced dermatitis might contribute to regrowth in alopecia areata. Larger, double-blind, placebo-controlled trials are needed.

## Bexarotene

In a randomized bilateral half-head study, hair regrowth of at least 50% on treated sites was noticed in only 26% of patients treated with 1% bexarotene gel.<sup>36</sup> Mild irritation is a common side effect.

## Capsaicin

In a nonblinded randomized study, 9.5% of patients with alopecia areata showed cosmetically acceptable hair regrowth after 12 weeks of applying capsaicin ointment.<sup>37</sup>

## Second-line therapies

### Sulfasalazine

Sulfasalazine is a combination of sulfapyridine and 5-aminosalicylic acid linked by a diazo bond. Sulfasalazine has both immunomodulatory and immunosuppressive actions

that include suppression of T cell proliferation and reducing the synthesis of cytokines, including interleukin (IL) 6, 1, and 12, tumor necrosis factor alpha, and antibody production.<sup>38</sup> Sulfasalazine has been used safely as a long-term treatment of various inflammatory and autoimmune diseases, including inflammatory bowel disease and rheumatoid arthritis. Several case reports and case series showed good hair regrowth with sulfasalazine in the treatment of alopecia areata.

In an uncontrolled prospective trial of sulfasalazine in 39 patients with persistent alopecia areata, hair regrowth of more than 60% was achieved in 25.6% of patients. A moderate response was seen in 30.7% of patients.<sup>39</sup> Also, in another uncontrolled open-label study, complete hair regrowth was reported in 27.3% of subjects.<sup>40</sup> Sulfasalazine was started at 500 mg twice daily for one month, 1 g twice daily for one month, and then 1 g three times daily.<sup>41</sup> Side effects to sulfasalazine include gastrointestinal distress, dizziness, and headache.<sup>39</sup> Gastrointestinal symptoms can be minimized by using enteric-coated tablets, taking the medication with food, and starting at lower doses. Initially, patients should have a complete blood count, liver function tests, creatinine, and glucose-6-phosphate dehydrogenase level measurement. Complete blood counts and liver function tests should be performed at 2–4-week intervals during the first three months of therapy. The reported relapse rates are 22.7%–45.5%.<sup>39,40</sup>

## Photochemotherapy

The success rate for oral and topical psoralen plus ultraviolet A (PUVA) ranged from 15% to more than 70%.<sup>42,43</sup> PUVA-turban is a method of administering a dilute psoralen solution (8-methoxypsoralen 0.0001%) selectively to the scalp for 20 minutes using a cotton towel as a turban. The patient's scalp is then exposed to ultraviolet A radiation.<sup>44</sup> Treatment sessions are performed two or three times per week. PUVA-turban has been shown to be effective in about 70% of treated patients.<sup>44,45</sup> During a follow-up period of 15 months after PUVA-turban therapy, recurrences of alopecia areata were observed in 26% of responders.<sup>44</sup> PUVA-turban therapy lacks the systemic side effects of oral PUVA and can be considered as alternative therapy for patients with alopecia areata.

## Excimer laser

In a treatment of 42 alopecia areata patches with the 308 nm excimer laser, hair regrowth was observed in 41.5% of treated areas.<sup>46</sup> Hair regrowth was noticed to begin to appear during the second month of therapy. No regrowth of hair was noted on the control patches. Laser therapy was administered twice

a week for a maximum of 24 sessions. Apart from erythema at the treated sites, there were no significant adverse effects. Relapses of alopecia areata were observed in two patients with patchy alopecia areata of the scalp who had shown complete regrowth earlier. Also, the use of excimer laser in children with alopecia areata has been reported to have a good success rate.<sup>47</sup>

### Fractional photothermolysis laser

Good hair regrowth was achieved with fractional Er: Glass laser in a single case report.<sup>48</sup> Randomized controlled trials in a larger number of patients are required to confirm the efficacy of this modality of treatment.

## Third-line therapies

### Systemic corticosteroids

Systemic corticosteroids are one of the commonly prescribed therapies in patients with extensive alopecia areata. Various forms of corticosteroids have been used in different regimens. In one study, a once-monthly oral pulse of 300 mg prednisone induced a complete response in 41% of patients.<sup>49</sup> A similar effect has been reported in a placebo-controlled trial of oral prednisolone 200 mg once weekly in the treatment of extensive alopecia areata.<sup>50</sup> The relapse rate was 25%, and side effects of the therapy were noted in 55% of patients.<sup>50</sup> In a comparative trial, the response rate was better in patients treated with intramuscular triamcinolone acetonide 40 mg once monthly than in those treated with oral dexamethasone 0.5 mg/day.<sup>51</sup> In the same study, impairment of adrenocortical reserve was seen in 23% of the intramuscular triamcinolone acetonide group and in 7% of patients treated with oral prednisolone pulse therapy of 80 mg for 3 consecutive days once every 3 months. In a study of 139 patients treated with pulse corticosteroid therapy, a good response was achieved in 59.4% of patients with recent-onset disease (duration of alopecia areata up to 6 months) in comparison with 15.8% of subjects who had had alopecia areata for more than 6 months.<sup>52</sup> Alopecia totalis and alopecia universalis are far less responsive to this therapy than patchy alopecia areata.<sup>53</sup> The use of systemic corticosteroids is limited by their side effects (hyperglycemia, weight gain, hypertension, adrenal suppression, dysmenorrhea, immunosuppression, and acneiform eruption)<sup>50,54</sup> and the high relapse rate (14%–100%).<sup>51,55,56</sup>

### Methotrexate

In a long-term follow-up study of methotrexate in 33 patients with alopecia areata, complete hair regrowth was achieved

in 57% and 63% of patients who used methotrexate alone or with low doses of oral corticosteroids (prednisone 10–20 mg/day), respectively.<sup>57</sup> Thirty percent of patients had partial hair regrowth. The weekly dosages of methotrexate were 15–25 mg. The onset of hair regrowth was seen after a median delay of three months. Recurrences of alopecia areata after a decrease of the methotrexate dose or after stopping treatment were observed in 57% (8/14 cases) of responders. In a retrospective trial of methotrexate in 14 children with alopecia areata, approximately one third of patients experienced a clinically relevant therapeutic response.<sup>58</sup> The mean age of the patients was 14.7 (range 8–18) years. Adverse effects to methotrexate include persistent nausea, transient elevation of hepatic enzymes, and leucopenia.

### Cyclosporine

The success rate with oral cyclosporine is 25%–76.6%.<sup>59,60</sup> A recent study showed that a good response to oral cyclosporine can be predicted if the serum level of IL 18 is elevated and the level of soluble IL 2 receptor is low.<sup>61</sup> The use of oral cyclosporine in patients with alopecia areata is not generally favored due to its adverse event profile (nephrotoxicity, immune suppression, and hypertension) and a high relapse rate (up to 100%).<sup>62</sup> Also, alopecia areata incidence has been reported in several organ transplant patients receiving cyclosporine.<sup>63–66</sup> Although hypertrichosis is a documented side effect of oral cyclosporine,<sup>67</sup> a good response has not been achieved by using topical cyclosporine in humans.<sup>68,69</sup>

### Azathioprine

Azathioprine, a thiopurine analog immunosuppressive drug, has been used to treat a vast array of autoimmune diseases. It inhibits DNA synthesis and thus decreases proliferation of cells, especially T and B lymphocytes. Azathioprine also decreases the number of Langerhans cells and other antigen-presenting cells in the skin. In a recent pilot study of 20 patients treated with azathioprine 2 mg/kg/day as monotherapy, mean hair regrowth was 52.3% ± 38.4%.<sup>70</sup> These results need to be confirmed in large-scale, randomized, controlled studies.

### Biologics

Although tumor necrosis factor alpha is implicated in the pathogenesis of alopecia areata, there are several reported cases that have shown either development of alopecia areata or complete failure to respond to different tumor necrosis factor alpha inhibitors, including adalimumab,<sup>71,74</sup> infliximab,<sup>75,76</sup> and etanercept.<sup>77–79</sup> In a prospective trial of

17 patients with alopecia areata, Strober et al concluded that etanercept does not effectively treat moderate to severe alopecia areata.<sup>80</sup> Also, in a placebo-controlled study, Price et al showed that efalizumab, an anti-CD11a antibody, is not effective in the treatment of alopecia areata.<sup>81</sup> Some clinical trials are ongoing to evaluate the efficacy of the newer biologic therapies in the treatment of alopecia areata.

## Psychological support

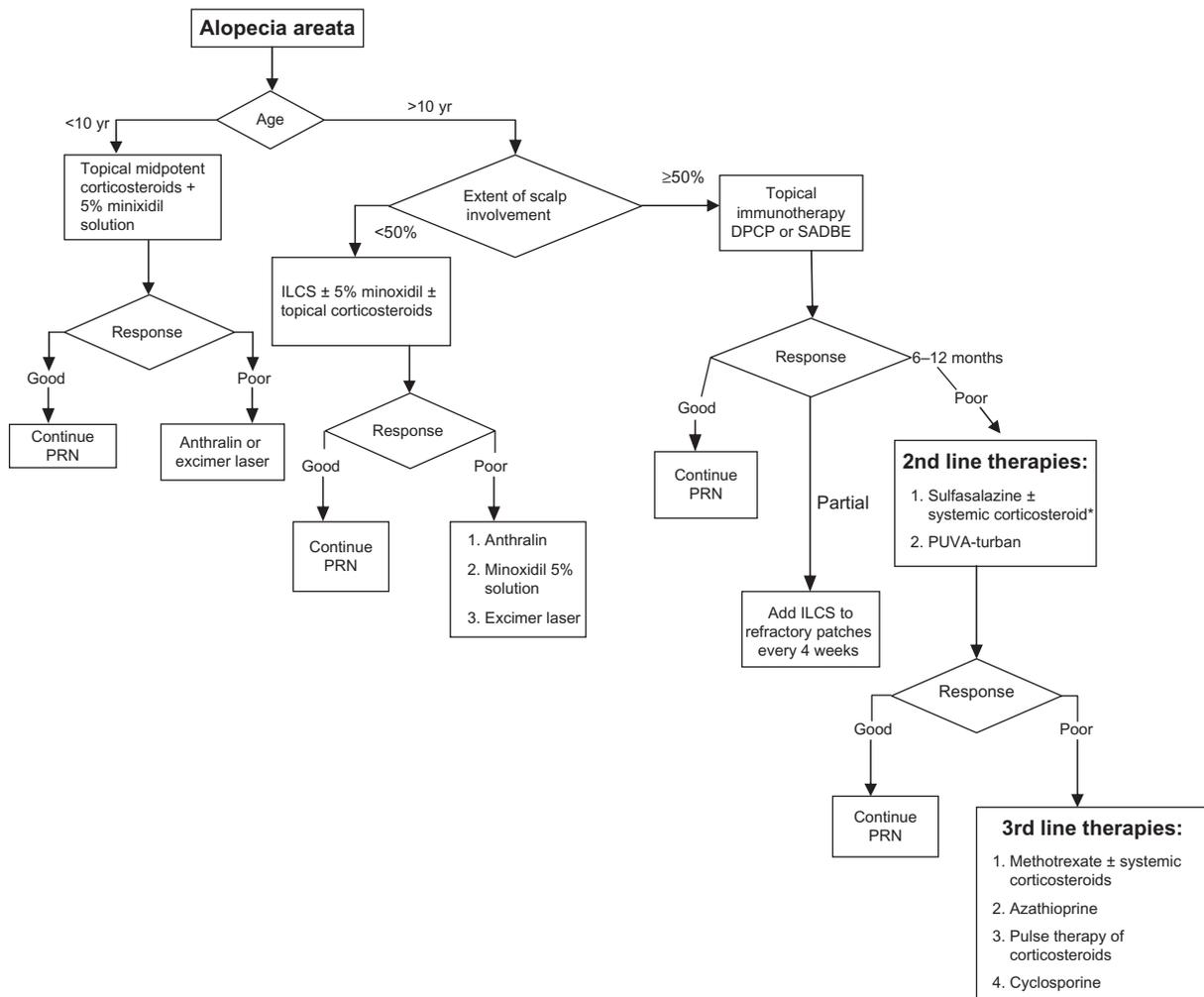
Alopecia areata is considered to be an example of a psychosomatic disorder, leading to dramatic and devastating emotions which can negatively impact patient self-esteem, body image, and self-confidence.<sup>82</sup>

One important step that should not be overlooked during the course of management of alopecia areata is offering psychological support to foster increased self-esteem and adaptation to this disease. Helping patients with alopecia

areata cope with depression and an unpredictable disease like alopecia areata can be achieved by several ways, including education of the patient about the nature of disease, psychotherapy, hypnotherapy,<sup>83</sup> antidepressants,<sup>84,85</sup> and support groups. Hypnotherapy may significantly improve depression, anxiety, and quality of life, but not hair regrowth.<sup>86</sup> Patients with extensive disease may wear scalp prostheses, such as wigs, hairpieces, or other scalp coverings.

## Other therapies

Other therapeutic agents have been tried, with some degree of success. These modalities include aromatherapy,<sup>87</sup> a combination of topical garlic gel and betamethasone valerate cream,<sup>88</sup> topical azelic acid,<sup>89</sup> oral zinc supplementation,<sup>90-92</sup> topical onion juice,<sup>93</sup> a simvastatin-ezetimibe combination,<sup>94,95</sup> inosiplex,<sup>96-98</sup> and intralesional injections of candida antigen.<sup>99</sup>



**Figure 1** Treatment plan for AA.

**Note:** \*Systemic Corticosteroids are used as a bridge therapy.

**Abbreviations:** DPCP, diphenylcyclopropanone; ILCS, intralesional corticosteroids; PRN, as needed; SADBE, squaric acid dibutylester.

These treatment modalities need to be confirmed in large-scale, double-blind, placebo-controlled trials.

There are other modalities of therapy that have not shown good efficacy. These agents include imiquimod,<sup>100,101</sup> topical calcineurin inhibitors,<sup>102–106</sup> botulinum toxin type A,<sup>107</sup> topical tri-iodothyronine ointment,<sup>108</sup> photodynamic therapy,<sup>109–111</sup> and topical 5-fluorouracil.<sup>112</sup>

## Management plan

Treatment options should be selected according to patient age and extent of disease. For patients younger than 10 years, a combination of 5% minoxidil solution twice daily with midpotent corticosteroids should be tried first. If there is no good improvement after 6 months, short-contact anthralin is considered as second-line therapy. Excimer laser can be used, particularly in patchy alopecia areata.

For patients older than 10 years of age with alopecia areata involving less than 50% of the scalp, intralesional triamcinolone acetonide injection (5 mg/cc) is the recommended option for treatment. If there is no good response after 6 months, other options can be tried, including potent topical corticosteroids under occlusion at night, 5% topical minoxidil twice a day, short-contact anthralin, and excimer laser.

If alopecia areata involves more than 50% of the scalp, topical immunotherapy with diphenylcyclopropenone is the first therapeutic option recommended by many experts in hair diseases. Intralesional injections of triamcinolone acetonide are used to treat persistent alopecic patches.

For patients who respond poorly to diphenylcyclopropenone and those who cannot use it, second-line therapies can be used. Several reviews of alopecia areata therapy suggest topical minoxidil and topical corticosteroids<sup>113–116</sup> but, as discussed earlier, the yield of these topical agents in the treatment of extensive alopecia areata is limited. Therefore, we suggest that patients with extensive resistant disease can use sulfasalazine with or without systemic corticosteroids. Systemic steroids are used as bridge therapy until the sulfasalazine takes effect. Treatment with sulfasalazine is generally well tolerated and characterized by a lower incidence of serious side effects in comparison with other systemic therapies like corticosteroids and methotrexate. The other second-line therapy is PUVA-turban. It is a well tolerated therapy with minimal local phototoxic side effects and without the systemic side effects of PUVA. These options are selected based on a balance between the efficacy and safety of these therapeutic agents.

If these therapies fail or are not tolerated, third-line therapeutic options can be discussed with patients in terms of the expected outcome of therapy and possible side effects.

These agents include methotrexate with or without a systemic corticosteroid, azathioprine, cyclosporine, and pulse therapy of corticosteroids. While using these drugs, close monitoring of patients is important to avoid possible side effects. A summary of an alopecia areata treatment plan is shown as an algorithmic approach in Figure 1.

## Disclosure

The author reports no conflicts of interest in this work.

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