Alopecia Areata: Treatment of Today and Tomorrow

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It is the aim of this article to review and appraise available data on treatments for alopecia areata (AA) according to the demands of evidence based medicine. Studies evaluating the efficacy of a treatment for AA should include appropriate controls, use cosmetically acceptable hair regrowth as a parameter for treatment success, include patients with AA totalis, universalis or extensive patchy AA, and exclude patients suffering from AA for less than 3 months. Moreover, the treatment must be safe over a prolonged period of time. Among the various therapeutic approaches presently available for AA, only treatment with contact sensitizers such as diphenylcyclopropenone or squaric acid dibutylester has been shown to be effective in studies that fulfill these criteria. Improved future treatments may be immunosuppressive or immunomodulatory targeting of the autoimmune pathogenesis of AA, or they may otherwise protect hair follicles from the injurious effects of inflammation. Such possible future therapeutic approaches include the incorporation of immunomodulatory agents into liposomes as an improved vehicle; inhibition of apoptosis mediated by the Fas-FasL system; inhibition of the lymphocyte homing receptor CD44v10; induction of tolerance. ***Key words: Evidence based medicine/T-cell/autoimmune disease/hair follicle. JID Symposium Proceedings 8:12–17, 2003***

Alopecia areata (AA) is characterized by patchy or sometimes total loss of scalp or body hair with waxing and waning of bald areas. Although acute phases of hair loss are followed by spontaneous hair regrowth in most patients, the disorder may persist for many years or even for life when severe. But even in these cases hair loss is potentially reversible, because the disease usually does not result in destruction of hair follicles or scarring. Therefore, every patient suffering from AA has the right to be treated according to the rules of evidence based medicine (EBM) (Epstein, 2001), which is the process of systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions (Rosenberg and Donald, 1995). It is the aim of this review to assess critically the published studies dealing with various therapies for AA and to determine which are most effective and safe.

There are about 600 publications, not to mention anecdotal reports, about treatment of AA published in the last 30 years. But "*the practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research*" (Sackett, 1996). Therefore, we define four criteria that help to identify publications that are the best available evidence:

1 Because AA is characterized by episodes of hair loss and regrowth and the spontaneous course of the disease cannot be predicted, any treatment study has to distinguish between spontaneous remission and therapeutic response. This is possible in a double-blind, placebo controlled study, which must include a large number of patients to yield statistically significant results. In topical approaches, however, the strictest criterion to exclude spontaneous remission is to treat every patient on one half of the scalp only. Only patients with substantially better hair growth on the treated side are allowed to be regarded as successfully treated. In patchy AA a large patch has to be treated unilaterally, because treatment of one patch with another patch as control does not exclude spontaneous hair regrowth. Half-side treatment can even be performed in a double-blind form by treating one side with the drug and the other with a placebo.

2 Hair regrowth in the treated area has to be substantial and cosmetically acceptable, because 'some regrowth' is not of practical benefit to the patient.

3 The prognosis of AA is influenced by several factors, in particular by the type and extent of AA (Weise *et al*, 1996; Wiseman *et al*, 2001) with a worse prognosis for patients with AA totalis or universalis or with extensive patchy AA as compared to limited patchy AA. According to the rules of EBM, we cannot accept the auxiliary hypothesis of a dichotomy between mild AA that can be 'successfully' treated with various doubtful approaches, such as topical corticosteroids, minoxidil or anthralin, and severe AA that cannot be treated with these drugs. Rather there is convincing evidence that these topical approaches do not exert any inhibitory effect on a possible spontaneous regrowth. Hence, studies evaluating a treatment for AA should preferably include patients with AA totalis, AA universalis and extensive patchy AA (>25% scalp hair loss).

4 The duration of the disease also has an influence on its prognosis. Because hair regrowth is more likely in AA of short duration, patients to be included in a study should have had AA for more than 3 months.

5 Any treatment has to be suitable for long-term therapy, because AA is a disease that can persist for many years or even for life. Hence, all therapeutic approaches showing severe side-effects in the long run are inappropriate.

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Abbreviations: AA, alopecia areata; DCP, diphenylcyclopropenone; SADBE, squaric acid dibutylester; DEBR, Dundee experimental bald rat; EAE, experimental autoimmune encephalomyelitis.

In summary, a study according to the demands of EBM should fulfill the following criteria:

1 Controlled study (placebo controlled with statistically significant results, or unilateral treatment)
2 Majority of patients with AA totalis, AA universalis or extensive patchy AA (>25% hair loss)
3 Duration of disease for more than 3 months
4 Cosmetically acceptable hair regrowth
5 No serious side-effects

CURRENT TREATMENTS FOR ALOPECIA AREATA

Immunosuppressive Treatments

Corticosteroids Among their various anti-inflammatory effects that are beyond the scope of this article, corticosteroids are known to exert a strong inhibitory effect on the activation of T lymphocytes. In consideration of the T_H-1 mediated immune attack on the hair follicle in AA, corticosteroids are potentially good candidates for the treatment of this disease.

Topical, intralesional, and systemic corticosteroids have been used to treat AA, with different rates of success and side-effects.

Topical corticosteroids Topical treatment with corticosteroid creams, ointments or lotions are frequently used for AA. However, only two placebo-controlled studies reported a treatment response (Pascher *et al*, 1970; Leyden and Kligman, 1972), but both studies do not fulfill the other criteria for evidence based treatment of AA. Furthermore, both studies were performed in the 1970s and they have not been confirmed by others over the last 30 years (Weitgasser, 1968; Verbov, 1973; Lehnert, 1974; Montes, 1977). Only one placebo-controlled study with an appropriate number of patients has been performed to date, but the rate of treatment success was not statistically significant (Charuwichitratana *et al*, 2000).

The failure of topical corticosteroids is most likely due to the insufficient penetration of topically applied drugs from ointments, creams or lotions into the hair bulb. Improving penetration by occlusion has been tried without success (Lehnert, 1974). Considering the lack of treatment response and the side-effects of topically applied corticosteroids, we conclude that topical corticosteroids are not an effective method of treating AA.

Intralesional corticosteroids Intralesional injection of corticosteroid crystal suspensions, primarily triamcinolone acetonide, has been used to treat AA for more than 40 years (Kalkoff and Macher, 1958). Several studies reported hair regrowth at the site of injection in the majority of cases (Kalkoff and Macher, 1958; Orentreich *et al*, 1960, Fülöp and Vajda, 1971; Porter and Burton, 1971; Abell and Munro, 1973; Frentz, 1977). Most of these studies tried to exclude spontaneous hair regrowth by comparing the injected sites of the scalp with uninjected areas, especially in alopecia totalis. However, in practice, it is impossible to treat the whole scalp by intralesional injections of corticosteroids and so this treatment is only indicated in patchy AA with longstanding bald areas. Apart from the painful procedure of injection, permanent atrophy can occur after injection. Taken together, intralesional injection of corticosteroids is a reasonable treatment in exceptional, selected cases of longstanding small patches of AA, but has potentially serious side-effects.

Systemic corticosteroids AA has been treated with systemic corticosteroids since 1952 (Dillaha and Rothman, 1952). Whereas, initially, oral corticosteroids were used daily or every other day for several months, this continuous use of corticosteroids is obsolete today. Doses that are required to maintain hair regrowth in AA are between 30 and 150 mg daily, giving rise to unacceptable side-effects such as hypertension, diabetes, immunosuppression, osteoporosis and proneness to thrombosis.

Since 1975 several authors have performed pulsed administration of corticosteroids in single doses, given once monthly in order to reduce the side-effects of corticosteroids to an acceptable level, but all studies which noted hair regrowth, were uncontrolled and the majority of patients had patchy AA (Perriard-Wolfensberger *et al*, 1993; Sharma, 1996; Friedli *et al*, 1998; Sharma and Muralidhar, 1998; Seiter *et al*, 2001). Moreover, other studies reported treatment failure after corticosteroid pulse therapy (Burton and Shuster, 1975; Schulz *et al*, 1996). Controlled studies should be conducted to prove the efficacy and long-term value of this treatment. Especially the efficacy in interrupting acute phases of rapid hair loss by pulsed administration of oral corticosteroids should be investigated. Based on the data presently available, pulsed administration of corticosteroids for AA cannot be recommended.

PUVA Several studies have examined treatment of AA with PUVA using either oral 8-methoxypsoralen (8-MOP) with ultraviolet A radiation (UVA) on the scalp or the whole body, or topical application of 8-MOP and UVA radiation on the scalp, including one study with topical application of psoralen via the PUVA-turban (Claudy and Gagnaire, 1983; Larkö and Swanbeck, 1983; Lassus *et al*, 1984; Mitchell and Douglass, 1985; Healy and Rogers, 1993; Taylor and Hawk, 1995; Behrens-Williams *et al*, 2001). Some studies seemed to have good results (Claudy and Gagnaire, 1983; Lassus *et al*, 1984; Healy and Rogers, 1993; Taylor and Hawk, 1995; Behrens-Williams *et al*, 2001), but there were no controls in any of the studies. Moreover, there were a large number of recurrences (between 30% and 50% of successfully treated patients) after initial hair regrowth, which strongly decreased the efficacy of PUVA treatment for AA (Claudy and Gagnaire, 1983; Lassus *et al*, 1984; Healy and Rogers, 1993; Taylor and Hawk, 1995). The high number of recurrences is most likely due to the fact that regrown hair inhibits UVA radiation from reaching the skin. Technical improvements such as a comb that emits UVA radiation have been tried, but so far no results have been reported. Unfortunately, continuous hair regrowth after an initial response has to be actively maintained for several years in most cases. Because of an increased risk for skin malignancies after long-term therapy, PUVA cannot be recommended for AA, even if technical improvements such as a UVA-comb should ultimately prove to be effective.

Immunomodulatory treatments

Diphenylcyclopropenone and squaric acid dibutylester AA has been treated with contact sensitizers for more than 20 years. Dinitrochlorobenzene (DNCB) was the first to be used (Happle and Echternacht, 1977), but because it has been shown to be mutagenic in the Ames test, it can no longer be recommended (Happle, 1979, 1985). Today diphenylcyclopropenone (DCP) or squaric acid dibutylester (SADBE), which are not mutagenic in the Ames test, are widely used in Europe and in Canada.

Treatment Treatment with contact sensitizers is preceded by sensitization of the patient with 2% DCP solution on a small area of the scalp. Two weeks later, treatment is initiated by applying a 0.001% DCP solution, followed by weekly applications of increasing concentrations until a mild eczematous reaction is obtained. In this way, an appropriate eliciting concentration of DCP is identified for each patient. This concentration is then applied once a week to induce a mild eczematous reaction characterized by itching and erythema, without blistering or oozing. SADBE is used in those patients who become tolerant to DCP. It is applied in the same way and shows similar rates of response.

Initial hair regrowth is usually visible after 8–12 weeks. Treatment must be continued once weekly until complete hair regrowth is obtained. Treatment intervals are then decreased, and, eventually treatment may be discontinued. However, if relapse occurs, treatment can be restarted immediately to stop further progression of AA and to induce renewed hair growth. At the Department of Dermatology, University of Marburg, treatment is always applied initially to half of the scalp and the other half

is left untreated to exclude spontaneous hair regrowth coincident with treatment initiation. Treatment is continued on both sides only after the treated side has shown a response that is better than that of the untreated side.

Side-effects Mild eczematous reactions and enlargement of retroauricular lymph nodes are desired reactions and inherent to treatment. These are usually well tolerated if patients are informed that they are desired for the therapeutic effect. Undesired side-effects are noted in 2–5% of patients (Hoffmann and Happle, 1996). Vesicular or bullous reactions sometimes occur at the beginning of treatment before appropriate individual concentrations have been determined. Dissemination of allergic contact dermatitis, urticarial or erythema multiforme-like reactions may also occur (Perret *et al*, 1990), but these can be treated successfully with topical corticosteroids. Pigmentary disturbances such as postinflammatory hyperpigmentation with spotty hypopigmentation ('dyschromia in confetti') have been observed, especially in patients with dark skin, but these have resolved within 1 years after discontinuing treatment in most instances (van der Steen and Happle, 1992; Hoffmann and Happle, 1996). Apart from these acute and subacute side-effects, no long-term side-effects have been reported after 18 years of DCP (21 years of SADBE) treatment worldwide of about 10000 patients, including children. However, it should be borne in mind that DCP and SADBE are not approved therapeutic substances.

Studies More than 25 studies have been performed to test the efficacy of treating AA with contact sensitizers. The most significant controlled studies are listed in **Table 1**. In contrast to corticosteroid and PUVA treatment studies, the majority of studies with contact sensitizers were controlled, with most using an untreated side of the scalp as a control. When comparing response rates for various modalities, one should bear in mind that spontaneous regrowth is excluded in these controlled, within-patient studies, but not in the uncontrolled ones. Response rates of treatment with contact sensitizers varies from 29% to 78% (see **Table**). The differences may be explained in part by the different extent and duration of AA prior to treatment for the patients in each study, and in part by differences in methods of treatment. However, the median response rate of all studies is 51%, rendering contact sensitizers an effective therapeutic tool for AA according to the demands of EBM.

How contact sensitizers act in treating AA is still not fully understood, but recent studies have contributed useful information. This has been discussed in detail elsewhere (Freyschmidt-Paul *et al*, 2001; Happle *et al*, 1986). Briefly, the specific interaction of $CD8^+/CD4^+$ T lymphocytes with dendritic cells and MHC class I/MHC class II positive hair follicle keratinocytes leading to AA may be interrupted by treatment with a contact sensitizer, by introducing tolerogenic cytokines T-cells or cytokines.

Other treatments

Irritant contact dermatitis – anthralin While treatment of AA using allergic contact dermatitis has proven to be effective, treatment of AA with an irritant contact dermatitis has never been shown to be successful in a controlled study. In a half-side controlled study, using 0.1% anthralin to produce a mild irritant contact dermatitis, no differences between treated and untreated sides were observed (Nelson and Spielvogel, 1985). Therefore, anthralin cannot be recommended for treatment of AA.

Minoxidil Because the antihypertensive agent minoxidil causes hypertrichosis as a side-effect, Weiss *et al* attempted to use it as a treatment for various forms of hair loss, including alopecia areata (Weiss *et al*, 1984). But none of the studies that have claimed success with minoxidil fulfillled the criteria of evidence based treatment (Weiss *et al*, 1984; Fiedler-Weiss *et al*, 1986; Price, 1987a, b; Ranchoff *et al*, 1989).

Six other placebo-controlled studies performed by various groups failed to show statistically significant differences between the placebo and minoxidil (White and Friedmann, 1985; Frentz, 1984; Maitland *et al*, 1984; Vanderveen *et al*, 1984; Vestey and Savin, 1986; Fransway and Muller, 1988). In three of these studies cosmetically acceptable hair regrowth was not observed in any patient (White and Friedmann, 1985; Vanderveen *et al*, 1984; Fransway and Muller, 1988).

When the pathophysiological demands of AA are considered, it is not surprising that minoxidil does not induce hair regrowth, because it exerts no effect on the extent or composition of the perifollicular infiltrate (Khoury *et al*, 1992). A nonspecific action of minoxidil is very unlikely to induce hair regrowth, because each growing anagen hair follicle will be attacked by the

Table 1. Treatment of AA with contact sensitizers, studies according to the demands of EBM

		Clinical form of AA (number of patients)					
Reference	Contact Sensitizer	Patchy AA	AA totalis	AA universalis	Controlled study	Number of patients	Cosmetically acceptable hair regrowth
Happle *et al*, 1983	DCP	5	22	0	Yes (ULT)	27	**68**
Happle *et al*, 1984	DCP	8	37	0	Yes (ULT)	45	**58**
Ochsendorf *et al*, 1988	DCP	18	8	1	Yes (ULT)	27	**37**
Macdonald Hull and Norris, 1988	DCP	8	20	0	Yes (ULT)	28	**29**
Monk, 1989	DCP	0		14	Yes (ULT)	14	**43**
Steen van der, *et al*, 1991	DCP	78	32	29	Yes (ULT)	139	**50.4**
Macdonald Hull *et al*, 1991b	DCP	4	8	0	Yes (ULT)	12 children	**33**
Macdonald Hull *et al*, 1991a	DCP	33	45	0	Yes (ULT)	78	**55**
Hoting et Boehm, 1992	DCP	11	20	14	Yes (ULT)	45	**51**
Gordon *et al*, 1996	DCP	12	36	0	Yes (ULT)	48	**38**
Schuttelaar *et al*, 1996	DCP	10	16	0	Yes (ULT)	26 children	**32**
Weise *et al*, 1996	DCP	43	22	40	Yes (ULT)	105	**48**
Cotellessa *et al*, 2001	DCP	14	42	0	Yes (ULT)	56	**48**
Wiseman *et al*, 2001	DCP	113	35	0	Yes (ULT)	148	**77,9**
Happle *et al*, 1980	SADBE	26	27	0	Yes (ULT)	53	**70**
Case *et al*, 1984	SADBE	11		10	Yes (ULT)	21	**52**
Caserio 1987	SADBE	2	5	7	Yes (ULT)	14	**29**
Micali *et al*, 1996	SADBE	129	8	0	Yes (ULT)	137	**64**

ULT, unilateral treatment, untreated side serves as control.

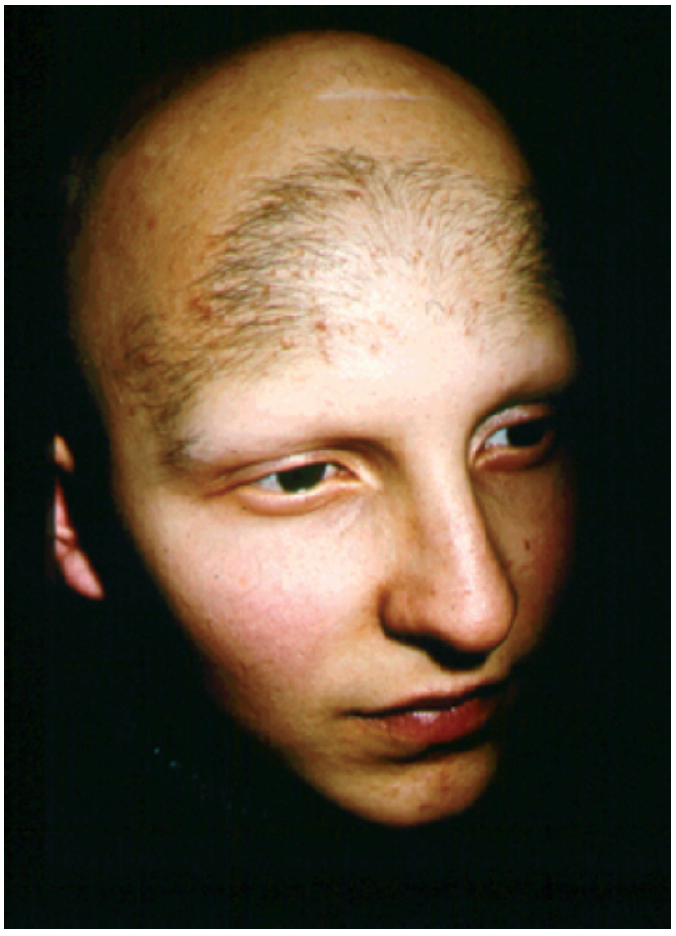

Figure 1. Evidence for complete ineffectiveness of topical minoxidil in AA. This 12-year-old girl applied 3% minoxidil to her hairless scalp. After 4 months, conspicuous hair growth was induced on her unaffected forehead, whereas the affected scalp remained completely bald (courtesy of Dr Claus W. Meisel, Nuremberg, Germany).

immune response if there is no immunomodulation or immune suppression (**Fig 1**).

In summary, minoxidil is not useful in treating AA.

EXPERIMENTAL THERAPEUTIC APPROACHES FOR ALOPECIA AREATA

FK506 FK506 (tacrolimus) is an immunosuppressive agent that can be applied topically to the skin. FK506 suppresses IL-2 production and release in activated T cells. Subsequently, activation and proliferation of T cells are inhibited (Schreiber and Crabtree, 1992). Therefore, FK506 is a promising candidate for the treatment of AA. Moreover, topical application of FK506 also has a hair growth stimulatory effect, independent of its T cell suppressive effect (Yamamoto *et al*, 1994).

In the DEBR model of AA and in AA affected C3H/HeJ mice, topically applied FK506 induces hair regrowth (McElwee *et al*, 1997; Freyschmidt-Paul *et al*, 2001), accompanied by reduced peri- and intrafollicular infiltrates of $CD4^+$ and $CD8^+$ T cells and decreased expression of MHC class I, MHC class II and ICAM-1 on hair follicle epithelium. These encouraging results obtained in animal models suggested that topical application of FK506 could be effective in the treatment of human AA. However, our own patients topically treated with tacrolimus did not show any benefit. This is most likely due to the insufficiency of the vehicle to transport FK506 to the hair bulb.

FUTURE THERAPEUTIC APPROACHES

AA is considered to be a T cell mediated autoimmune disease of the hair follicle (McElwee *et al*, 1999; Freyschmidt-Paul *et al*, 2001), but the detailed pathogenesis of AA is thus far poorly understood. Therefore, it is unlikely that a treatment inhibiting the onset of AA will be developed in the foreseeable future. Rather, future therapeutic approaches should focus on limiting the expression of the disease by down-regulating autoreactive cells in the lymphocytic infiltrate by an immunosuppressive or immunomodulatory action or by protecting the hair follicle from the injurious effects of the inflammation.

In developing new treatments for AA, the nature of the disease must be considered. As outlined above, therapeutic approaches must be suitable for long-term therapy and should not cause severe side-effects. Because the inflammatory process prevails in and around the bulbar region of the hair follicle, any effective drug must act in this region. When applied topically, it must penetrate into the subcutaneous fatty tissue. Otherwise it has to be given systemically.

Macrolides of the Ascomycin Type Out of the group of macrolides of the ascomycin type, topically applied SDZ ASM 981 has been used successfully to treat psoriasis and allergic contact dermatitis (Paul *et al*, 2000). It inhibits the synthesis of Th1 and Th2 cytokines. Because the pathogenesis of AA is Th1 mediated, topical SDZ ASM 981 may be a candidate for AA. Controlled studies to challenge this hypothesis have not been reported.

Liposomes Another novel approach in treating AA is to create a vehicle that allows penetration to the subcutaneous fat where the bulbs of anagen hair follicles are located and where the pathomechanism takes place. Such a vehicle could be used to carry, for example, a steroid to the peribulbar lymphocytic infiltrate, thus making topical steroids, which are ineffective in current formulations, a useful treatment. Other immunosuppressive agents, such as FK506, might be effective in such a vehicle, also. At present, liposomes seem to be the best candidate as a vehicle topical treatment. Topically applied liposomes have been shown to deliver melanin, proteins, genes and various small molecules selectively to hair follicles and hair shafts of mice *in vivo* (Li and Hoffman, 1997). Liposome-targeting of molecules to human hair follicles has been demonstrated in human scalp in histoculture (Li and Hoffman, 1995). However, future experiments have to show whether liposomes are able to deliver molecules to the hair bulb in human scalp *in vivo.*

Anti-CD44v10 antibodies Our group has shown that the developement of AA in the C3H/HeJ mouse can be inhibited by application of an anti-CD44v10 antibody (Freyschmidt-Paul *et al*, 2000). This antibody most likely inhibits CD44v10 mediated homing of $CD8^+$ T cells into the skin. Therefore, application of anti-CD44v10 antibodies might be a therapeutic tool to inhibit the development of AA. However, such antibodies have so far never been used in humans, and nothing is known about their side-effects.

Inhibition of the Fas-FasL system Induction of hair follicle apoptosis by the Fas-FasL system seems to be involved in the pathogenesis of AA (Bodemer *et al* 2000; [1]). Therefore, inhibition of the Fas-FasL system might protect hair follicles from injury caused by the inflammatory infiltrate. However, such treatment could only be applied topically and specifically limited to hair follicles, because systemic inhibition would disturb essential control mechanisms of lymphocyte homeostasis.

[1]Freyschmidt-Paul P, McElwee K, Botchkarev V, Sundberg J, Happle R, Hoffmann R: The role of Fas and Fas Ligand in alopecia areata of C3H/HeJ mice. *J Invest Dermatol* 117:431 2001 (abstr.)

Tolerance While the above-mentioned therapeutic approaches target symptoms, the induction of tolerance to autoimmune diseases comes close to a causal treatment. At present the best understood way to induce tolerance is through oral administration of an antigen. Studies in rheumatoid arthritis suggest that induction of oral tolerance is a safe and effective (Garcia and Weiner, 1999). The major problem in developing a protocol for induction of tolerance in AA is to find a suitable antigen, because at present the autoantigen of AA is unknown. One possibility to circumvent this problem is to use an antigen that is found in the hair follicle close to the morphological location of the original autoantigen. Induction of oral tolerance against this antigen would lead to the development of regulatory T cells that migrate to a target tissue (the hair follicle) and secrete antigen-nonspecific cytokines after being triggered with the fed antigen in the hair follicle again. These cytokines, suppress inflammation in the microenvironment where the fed antigen is localized. This 'bystander suppression' has been demonstrated to be effective in various animal models of autoimmune diseases such as experimental autoimmune encephalomyelitis (EAE), arthritis, and diabetes (Garcia and Weiner, 1999). The immunosuppresion after induction of tolerance is restricted to the site where the antigen is located and systemic immunosuppression can be avoided.

CONCLUSION

AA is today considered to be caused by a T-cell mediated autoimmune attack of the hair follicle. According to the rules of evidence based medicine, treatment with contact sensitizers such as DCP or SADBE is the only approach with proven effectiveness. All other methods presently available are either completely ineffective, ineffective in the long run, or associated with unacceptable side-effects. Hence, treatment with potent contact sensitizers is presently the best available approach for AA. Pulsed administration of oral corticosteroids has so far not been tested according to the rules of evidence based medicine, but this should be performed in the future. As long as no causal treatment is available, future approaches should focus on a more specific targeting of the underlying pathomechanism with a topical action around the hair bulbs and without serious side-effects. Possible new therapeutic developments may include incorporation of drugs in liposomes, macrolides of the ascomycin type, anti-CD44-v10 antibodies, inhibition of the Fas-FasL system, induction of tolerance.

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