

Intralesional triamcinolone acetonide for alopecia areata: does dilution matter?

Acetonido de triancinolonaintralesional na alopecia areata: a diluição importa?

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Abstract

Alopecia areata (AA) is a chronic, remitting, non-scarring form of alopecia, which can be associated with significant emotional distress. Intralesional corticosteroids, particularly triamcinolone acetonide, remain first-line therapy in adults with limited, patchy alopecia areata. However, the optimal concentration of intralesional corticosteroids has not yet been fully elucidated. In this manuscript, we examine current evidence about this matter to guide clinical decision-making.

Keywords: Triamcinolone acetonide. Concentration. Dilution. Alopecia areata. Hair regrowth.

RESUMO

A alopecia areata (AA) é uma forma crónica e remitente de alopecia não cicatricial, que se pode associar a stress emocional significativo. Os corticosteroides intralesionais, particularmente o acetono de triancinolona, mantêm-se a terapêutica de primeira linha nos adultos com alopecia areata limitada, em placas. No entanto, a concentração ideal do corticosteroide intralesional ainda não foi devidamente estabelecida. Neste artigo, analisamos a evidência existente sobre este tema, de forma a orientar a decisão clínica.

Palavras-chave: Acetonido de triancinolona. Concentração. Diluição. Alopecia areata. Repovoamento capilar.

Introduction

Alopecia areata (AA), is a chronic, remitting, non-scarring, presumed autoimmune disease of the hair follicles leading to hair loss. AA has a lifetime prevalence of 1.7% and is frequently associated with significant emotional distress. The presence of well-demarcated, hairless patches with yellow dots and

short broken hairs (exclamation mark hairs) around the margins is highly diagnostic¹⁻⁴.

The choice of treatment depends on the extent of hair loss, previous treatment responses, and the patient's age. For the treatment of localized AA with less than 50% of scalp involvement in adults, intralesional (IL) corticosteroid injection, oral corticosteroids, topical calcineurin inhibitors, and local immunotherapy

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(diphencyprone, anthralin) are considered the best choice^{1,5-7}.

Triamcinolone acetonide (TA) remains the first-line IL corticosteroid therapy in adults with limited, patchy AA.

The use of IL corticosteroids for the treatment of AA varies between centers and the dilutions and doses of IL injections differ according to the experience of the physician^{1,8}. Typically, 2.5 and 5 mg/mL TA concentrations are recommended for the face (beard, eyebrows) and scalp, respectively⁹.

Still, the current literature is mostly limited to case series with small sample sizes and heterogeneous patient populations³.

Herein, we examine current evidence about the best triamcinolone concentration to guide clinical decision-making.

Intralesional corticosteroids

Intradermal corticosteroid injections have been used for the treatment of alopecia areata for many years. Kalkoff & Macher (1958)¹⁰ were the first to report a series using hydrocortisone. Subsequently, Orentreich et al. (1960) described injections of insoluble forms of prednisolone, hydrocortisone, and fludrocortisone as a practical method to treat AA¹¹, and Gombiner & Malkinson (1961) reported the use of triamcinolone 10 mg/mL¹².

Porter and Burton (1971) described the benefit of IL injections of 10 mg/mL TA and 5 mg/mL triamcinolone hexacetonide^{13,14}.

A previous open-label randomized study comparing the efficacy of intralesional triamcinolone acetonide (ITA) (10 mg/mL), topical bethametasone valerate foam, and tacrolimus ointment for the treatment of localized AA showed that hair regrowth within 12 weeks was best achieved in the ITA group^{15,16}. A meta analysis of 12 studies reported ILA as the most effective treatment in patients with limited AA and a shorter duration of disease, with a response rate ranging from 60 to 95%^{8,17}. These studies confirmed IL corticosteroids as a valuable therapeutic tool in AA.

IL corticosteroid injection seems to affect local cytokine expression leading to a gradual decrease in type 1 and type 2 cytokines and IL-23 in parallel with clinical improvement, suggesting that direct suppression of the local immune response is the main mechanism of action¹⁸.

Despite being less potent than betamethasone dipropionate (BD) (0.6 mg of BD corresponds to 4 mg/dL of TA), the low solubility and consequent

slow absorption of TA ensures maximum action and minimal systemic effects, which, along with its relatively low cost, make it the most popular among all available steroids^{1,8,19}.

Injection technique

Corticosteroid is injected into the dermis, with a 0.5-inch long, 30-gauge insulin injector, or a jet injector¹. The injection is mostly applied at 4-6 week intervals in amounts of 2-3 cc in each session over a treatment duration ranging from 6 weeks to 6 months^{3,16}. An injection of less than 0.1 cc is recommended for each injection point¹. It is estimated that an injection of 0.05–0.01 cc will produce a tuft of hair growth about 0.5 cm in diameter². One should not exceed a maximum dose of 20 mg per monthly session⁹.

Concentrations studied

The efficacy of different IL corticosteroid concentrations has been well documented in multiple studies (Table 1). A higher IL corticosteroid index (IL corticosteroid received/ severity score) was proved to correlate with a better hair growth response^{1,20}. Though, the best steroid dilution has not been fully elucidated yet.

The concentration of IL corticosteroids tends to vary from 2.5 to 10 mg/mL in different reports^{1,21-23}. Typically, 2.5 and 5 mg/mL triamcinolone acetonide concentrations are recommended for the face (beard, eyebrows) and scalp, respectively⁹.

Lower concentrations (2.5-3.3 mg/mL)

Ustuner et al. enrolled in one of the few studies comparing the clinical efficacy and safety of different dilutions of ITA (3.3, 5, and 10 mg/mL) and BD. They observed that the injection of four-fold diluted TA (10 mg/dL) was more effective than the 12-fold diluted solution (3.3 mg/mL)¹.

On the other hand, Chu et al. found the injection of 2.5 mg/mL TA as beneficial as the 5 or 10 mg/mL injection⁹. Moreover, skin atrophy was more frequent with 10 mg/mL TA. Thus, the authors advised injection of 2.5 mg/mL TA for limited, patchy alopecia areata involving less than 50% of the scalp⁹.

Another recent study compared the results of ITA 2.5 mg/mL with betamethasone 0.375 mg/mL and betamethasone 1.75 mg/mL, and 0.9% saline.

Table 1. Characteristics of the studies included and treatment results of triamcinolone acetonide in alopecia areata

Authors/ publication year	Study design	Number of patients	ITA concentration	Frequency, number and duration of treatments	Definition of response	Results
Abell and Munro 1972 ¹³	Prospective cohort	84	5 mg/mL	Weekly/twice weekly; 3 treatments	Not defined	86% regrowth at 6 weeks 62% 12 weeks
Porter and Burton 1971 ¹⁴	Prospective cohort	17	10 mg/mL	Single injection	Not defined	64% acceptable hair regrowth
Frentz 1977 ²⁵	CCT	12	5 mg/mL	Every 4 weeks 2-4 treatments	subjective	50%
Narahari 1996 ²⁸	CCT	37	10 mg/mL	Every 2 weeks Up to 2 months	Uniform eruption of hair follicles	84%
Kubeyinje and C'Mathur 1997 ³⁷	Open-label CCT	58	40 mg (nonspecified dilution)	Monthly 4 months	> 90% regrowth	67% ITA alone; 86% for ITA + Tretinoin 0.05% cream
Kubeyinje 1994 ³⁸	Prospective cohort	62	40 mg (nonspecified dilution)	Monthly 12 months	Complete hair regrowth	68%
Wahab 2006 ²⁶	Prospective cohort	40	3-5 mg/mL	Monthly 3-5 months	Complete hair regrowth	65%
Kuldeep et al. 2011 ¹⁵	RCT	25	10 mg/mL	Every 3 weeks 12 weeks	> 75% hair regrowth	60%
Chang et al. 2009 ³¹	Retrospective case series	10	5-10 mg/mL	Every 4-6 weeks	Complete/nearly complete cosmeti- cally acceptable	60%
Ganjoo and Tappa 2013 ²⁷	Prospective cohort	65	5 mg/mL	Every 4 weeks 24 weeks max.	Semi-quantitative regrowth scale	47% (12 wks) 95% (24 wks)
Chu et al. 2015 ⁹	double-blind placebo- controlled pilot study	4	2.5 mg/mL 5 mg/mL 10 mg/mL	Every 6 weeks 36 weeks	Folliscope imaging device *	No statistically significant difference in hair density/ caliber between concen- trations
Arminia et al 2015 ³⁰	Retrospective cohort	120	5 mg/mL	Every 3 weeks 12 weeks	> 60% hair regrowth	83.3%
Devi et al. 2015 ³²	RCT	113	10 mg/mL	Every 3 weeks 12 weeks	Not defined	74.3%
Kaur et al. 2015 ²⁹	Prospective cohort	40	2.5 mg/mL	Every 3 weeks 6 weeks	> 50% hair regrowth	67.5%
Malick et al. 2018 ³³	Prospective cohort	100	10 mg/mL	Monthly 3 months	> 50% hair regrowth	75%
Ustuner et al. 2017 ¹	RCT	89	3.3 mg/mL 5 mg/mL 10 mg/mL	Every 4 weeks 6 months	> 75% hair regrowth	56.3% (3.33 mg/mL) 87.9% (5 mg/mL) 97% (10 mg/mL)
Barbosa de Sousa 2020 ²⁴	Double-blind RCT	12	2.5 mg/mL	Every 4 weeks 12 weeks	Dermoscopy and photography**	38.7%

*Folliscope device CCL-215 USB, Sometech, Seoul, Korea.

** (ImageJ®).

CCT: controlled clinical trials; RCT: randomized control trials.

At 4 and 8 weeks of intervention, triamcinolone acetonide 2.5 mg/mL provided the best visual results²⁴.

Medium concentrations (5 mg/mL)

In 1973 Abell and Munro reported that 61% of patients with alopecia totalis treated with injections of 5 mg/mL

triamcinolone acetonide using the Porto Jet needleless showed regrowth at 12 weeks, compared with 7% of control subjects injected with isotonic saline. Of those with limited AA, 92% showed regrowth at 6 weeks, but only 71% maintained regrowth at 12 weeks¹³.

Frentz enrolled in the first controlled clinical trial (CCT) in 1977, using a split-body design to examine

12 patients with subtotal or universal AA. Half of the patients were treated with ITA 5 mg/mL, and the other half received contact ultraviolet radiation from a mercury arc source²⁵. Half of those receiving ITA had some regrowth compared with baseline, but growth decreased over time. The other half had no noticeable hair regrowth after injections. The authors concluded that ITA inhibited spontaneous regrowth.

A more recent prospective cohort study enrolled 40 patients who had failed to respond to potent topical steroids. ITA (3–5 mg/mL, 1 mL/cm²) was given monthly for 3–5 months. Complete hair regrowth occurred in 65% of all participants, with incomplete hair growth in a further 12%. Notably, in patients with “extensive alopecia”, only 25% of the patients achieved complete hair regrowth²⁶.

Regarding the pediatric population, Ganjoo and Thappa studied the usefulness of ITA 5 mg/mL concentration in children with AA involving < 50% of scalp and with less than three patches. About 95% of patients showed at least 75% regrowth in the area of the patch at 24 weeks²⁷.

Higher concentrations (10 mg/mL)

The efficacy of ITA (10 mg/mL) was compared with topical dithranol cream in 69 patients with a single lesion of AA. The satisfactory response was classified as “uniform eruption of hair from hair follicles in the lesional skin” and was described in 84% of patients receiving ITA and 59% of patients using topical dithranol. Though, at 12 months, patients treated with the injection had a statistically significant increase in relapse rates: 57% versus 12% in patients using dithranol. As a result, the author concluded that ITA induced a better but more temporary response rate compared with dithranol²⁸.

Kuldeep et al. performed a randomized prospective study in 2011 which analyzed 78 patients with three or fewer patches of AA and compared hair regrowth results in three different groups- one group treated with topical betamethasone valerate foam 0.1% (n = 28), another with ITA 10 mg/mL (n = 25) and another group received tacrolimus ointment 0.1% (n = 25). Sixty percent of those treated with ITA reached the end point of > 75% hair regrowth at 12 weeks, while this occurred only in 54% of those treated with topical betamethasone valerate foam, and no patient responded in the tacrolimus group¹⁵.

Yee et al. recently performed a systematic review and meta-analysis of all published data about the efficacy and tolerability of different concentrations of ITA for AA³.

The rates of hair regrowth were comparable in the 5 and 10 mg/mL concentrations (80.9%, p < 0.005 versus 76.4%, p < 0.005, respectively) while lower rates of hair regrowth (62.3%, p = 0.04) occurred when using concentrations < 5 mg/mL³.

In short, all studies, except one (which only included cases of extensive AA), supported intralesional steroids as a useful tool to treat AA, with varying degrees of success²⁵. This treatment option seems to be more effective in patients with limited alopecia and shorter disease duration^{1,8}.

ITA concentrations assessed varied from 2.5 to 10 mg/mL. Five studies included lower concentrations (2.5-3.3 mg/mL), with response rates ranging from 38.7 to 67.5%^{1,9,24,26,29}. Seven studies analyzed ITA concentrations of 5 mg/dL, with success rates ranging from 50 to 95%^{9,13,25–27,30,31}, and eight studies analyzed 10 mg/dL concentrations of ITA, with response rates of 60-84%^{1,9,14,15,28,31-33}. However, variations in method and frequency of administration limit the comparison of results between different studies.

The lack of consensus on this topic is explained, in part, by discrepancies regarding the definition of response (although the majority defined response to treatment as > 50% hair regrowth), as well as disparities among the characteristics of patients (different ages, gender, extent, and duration of alopecia). The scarcity of a standardized technique of injection and the absence of a placebo arm to control for spontaneous hair regrowth further contributes to this dilemma.

Furthermore, most studies compare the efficacy of ITA with other (non-injected) treatments or other injected steroids, with just four of them comparing the effectiveness of different concentrations of ITA^{1,3,9,24}.

Side effects

Skin atrophy at the site of injection is a consistent side effect of IL corticosteroid therapy. The risk is particularly high when higher concentrations or higher volumes are injected in the same site, but this usually resolves after a few months. The wrong technique (e.g., injection in subcutis) may also contribute to some cases of atrophy².

In their study, Ustuner et al. found cutaneous atrophy ratio after 6 months significantly superior in TA group compared to BD groups (85.7% vs 22.2%)¹.

Yee et al. described this side effect in 3.33% of subjects treated with 5 mg/mL concentration and 20% of subjects treated with 10 mg/mL³.

Apart from skin atrophy, one should also be aware of the risk of cataracts and raised intraocular pressure when corticosteroids are injected close to the eye. Anaphylaxis has been reported in two patients receiving TA for treatment of alopecia areata². Another rare complication is perilymphatic cutaneous atrophy³⁴.

Other reported side effects include slight discomfort and hemorrhage at the injection site, pustule, and folliculitis, and minor depression on plasma cortisol the day following triamcinolone injection^{1,13}.

Notably, there are some cases of glucocorticoid resistance in AA, which may be explained by decreased expression of thioredoxin reductase 1 in the outer root sheath^{35,36}.

Conclusion

Based on the existing research, concentrations of ITA between 5 and 10 mg/mL may offer the greatest benefit to patients with focal AA.

Using the lowest effective concentration minimizes local side effects of skin atrophy and likely reduces the potential for systemic absorption, allowing the treatment of more extensive scalp areas⁹. Therefore, the authors agree that ITA 5 mg/mL may have a better risk-benefit profile for scalp AA. Lower concentrations have proved to be less useful in most of the studies, unless when injecting the face (eyebrows/ beard) where these concentrations may be safer¹⁷.

Regardless of all the described studies, randomized controlled trials using a standardized technique are still needed to improve decision-making and better understand the individual and perceived benefits, risks, and tolerability of different concentrations.

What does this study add?

Triamcinolone acetonide is the first line of intralesional corticosteroid therapy for patients with limited, patchy alopecia areata.

Most of the existing literature compares intralesional triamcinolone acetonide with other (non-injected) treatments or other injected steroids. Just four studies compare the effectiveness of different concentrations of intralesional triamcinolone acetonide.

According to the current literature, concentrations of 5 mg/mL seem to be the best treatment choice for scalp

AA, and lower concentrations can be advised when injecting the face.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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