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The Efficacy and Adverse Effects of Corticosteroid Pulse Therapy in Alopecia Areata: A Review Article

Fatemeh Rastaghi[1], Roxana Kaveh[2], Nazafarin Yazdanpanah[3], Akram Sadat Sahaf[4], Najmeh Ahramyanpour[1,5]

1 Department of Dermatology, Afzalipour Hospital, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran
2 Student Research Committee, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran
3 Department of Dermatology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
4 Department of Dermatology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
5 Pathology and Stem Cell Research Center, Kerman University of Medical Sciences, Kerman, Iran

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Corresponding Author: Najmeh Ahramiyanpour, Assistant Professor of Dermatology, Department of Dermatology, Afzalipour Hospital, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran; Postal Code: 7616913555; Email: najme.pour@gmail.com

ABSTRACT

Introduction: Alopecia areata (AA) is a common, non-scarring, autoimmune hair loss disorder, varying in severity from small round hairless patches to the total loss of scalp or body hair. As steroid pulse therapy outcomes for AA vary, this study aimed to review the related literature regarding the efficacy, relapse rates, side effects, and prognostic factors associated with the response to different pulse corticosteroid treatments.

Methods: We performed a literature search on August 29, 2022, to provide an overview of the efficacy of pulse steroid therapy in patients with AA. The terms "pulse steroid therapy AND alopecia areata" and "pulse corticosteroid therapy AND alopecia areata" were searched on PubMed and Google Scholar.

Results: A total of 24 articles were assessed. There was no difference in outcomes and side effects between intravenous and oral pulse corticosteroid therapy. The relapse rate and efficacy depended on the time of AA onset, age, and AA type: improved outcomes and decreased relapse were linked with recent onset (<6 months), a younger age (<10 years), and the multifocal type of AA. Patients with a past medical history of atopy, nail pitting, or thyroid disease and those with severe forms of AA like alopecia totalis and alopecia universalis had the least improvement.

Conclusions: All kinds of mentioned systemic pulse corticosteroids effectively induce hair regrowth in AA. Betamethasone pulse seems to be the most effective agent (followed by intramuscular triamcinolone), especially in severe cases, but more side effects may accompany it. Combining this agent with other medications can reduce the dosage and side effects. Pulses of prednisolone and methylprednisolone are less effective but safer, as they have low relapse rates and adverse effects. A combination of them with other drugs can increase their efficacy.

Introduction

Alopecia areata (AA) is a common, non-scarring, autoimmune hair loss disorder with an estimated lifetime risk of approximately 2% [1-3]. Genetics and environment both play essential roles in the pathology of the disease, as almost 20% of the patients have a positive family history. In addition to the suggested autoreactive T-cell-mediated pathogenesis of the disease, psychological stress may also be heavily involved. The severity of AA ranges from small round hairless patches to the total loss of scalp or body hair (alopecia totalis/alopecia universalis), which can cause devastating psychosocial effects, such as major depression, anxiety, mood disorders, and social phobia [4-6].

Implementing and evaluating treatment protocols for AA is challenging due to the disease's uncertain pathogenesis and unpredictable remission rates [6]. The treatment should also cover the patient's psychological needs, making management more difficult. Topical, intralesional, and systemic agents have been used for AA, but the efficacy of the treatments varies widely [6-9]. One of the suggested treatments is corticosteroid therapy. Topical and intra-lesional corticosteroids are effective and well tolerated in patients with mild to moderate AA [4,6,10]. However, managing severe AA cases (alopecia universalis, totalis, and ophiasis) is more challenging [11]. Systemic corticosteroids are usually effective in these patients and can be administered via the intravenous, oral, or intramuscular route [12].

Objectives

In 1975, Burton and Shuster introduced corticosteroid pulse therapy for treating patients with AA to reduce the possible side effects of long-term use of corticosteroids and to increase the treatment's effectiveness. Since then, many scientists have aimed to optimize this type of therapy [10]. As steroid pulse therapy regimens and outcomes for AA vary, this study aimed to review the related literature regarding the efficacy, relapse rates, side effects, and prognostic factors associated with the response to different pulse corticosteroid treatments.

Methods

A literature search was performed on August 29, 2022, to review the efficacy of pulse steroid therapy in patients with AA. The terms "pulse steroid therapy AND alopecia areata" and "pulse corticosteroid therapy AND alopecia areata" were searched on PubMed and Google Scholar. All types of scientific publications matching the keywords were transferred to EndNote version 8 (Clarivate Analytics), and duplicates were removed. Two authors reviewed the articles independently based on their titles and abstracts. Subsequently, a third author performed an eligibility assessment of the full texts based on the inclusion and exclusion criteria. Inclusion criteria consisted of relevant full-text, English-written clinical trials. All case reports, editorials, conferences, commentaries, letters to editors, and review articles were excluded from the study. Poor quality trials were also excluded based on a Jadad scale of less than 3. In case of any conflicts, the senior author made the final decision and responded to each of the points raised in the screenings. After screening the data, a total of 24 articles were identified and included in this study. Then, two authors independently extracted and recorded the data in an Excel 2016 spreadsheet (Microsoft). The extracted features included the title, publication year, author names, year, sample size, mean age, type of treatment, assessments, outcomes, and side effects.

Results

The Efficacy of Intravenous Corticosteroid Pulse in Severe AA

The efficacy of intravenous steroid pulse was studied in ten articles. Among them, seven examined intravenous methylprednisolone, two assessed the combination therapy of methylprednisolone and cyclosporine, and one evaluated the combination of intravenous methylprednisolone and methotrexate.

Intravenous Methylprednisolone

Intravenous Methylprednisolone in Adults

Intravenous methylprednisolone was introduced to decrease the side effects of prolonged use of oral corticosteroids in

AA. Four studies evaluated the efficiency of intravenous methylprednisolone pulse therapy in a total of 224 adults with severe AA. They noticed that patients with recent onset of the disease (<6 months) responded better. Most patients with plurifocal AA or scalp involvement <50% showed significant hair growth (mostly complete remission), while none with alopecia universalis, totalis, or ophiasis showed more than 50% hair growth, even after six months of follow-up. They concluded that intravenous methylprednisolone is a safe and promising treatment in adults with plurifocal or recent-onset AA, with only mild adverse effects, while it is less effective in patients with alopecia universalis, totalis, or ophiasis [13-16]. In another study, Chao-Chun Yang et al reviewed 85 patients with severe AA treated with oral prednisolone pulse or intravenous methylprednisolone pulse. They noticed that the two treatments were equally effective in treating severe AA, as more than half of the patients experienced nearly 75% hair regrowth. Better results and less relapse were reported with earlier initiation of treatment, especially during the first year of disease onset. There was no significant difference in side effects between the two groups [17].

To study the long-term efficacy of intravenous pulse of methylprednisolone in treating severe AA, Staumont-Sallé et al assessed 60 patients who had received this treatment ten years earlier. They reported that patients who initially responded to therapy during the first six months had a milder disease in the next ten years, while those who were non-responders to therapy still had severe disease. Autoimmune thyroid disease and atopic disorders were more frequent in non-responders. This study considered intravenous methylprednisolone pulse therapy inefficient in treating severe AA and suggested other treatments for alopecia totalis and universalis [18].

Intravenous Methylprednisolone in Children

Friedland assessed the efficacy of intravenous methylprednisolone pulse in treating children with severe AA. Nearly 70% of patients experienced partial to complete remission, and a higher rate of hair growth was seen in multifocal AA patients. Surprisingly, 81% of responders had a relapse in the first year of treatment. Age at onset of fewer than ten years, disease onset below six months, and multifocal disease were recognized as good prognostic factors. No serious side effects were reported. This article concluded that all children with AA do not benefit from steroid pulse treatment; therefore, case selection plays a vital role in achieving optimal results and avoiding ineffective therapies [19].

Intravenous Methylprednisolone Combined With Cyclosporine

In a study by Shaheedi-Dadras et al, a 500 mg dose of intravenous methylprednisolone was administered in three consecutive doses monthly in addition to oral cyclosporine (2.5 mg/kg/day) for a treatment duration of 5–8 months. According to the results, only a third of the patients showed a hair regrowth rate of more than 70%. Patients with nail pitting or a positive history of atopy responded poorly. They suggested that this treatment can be effective in treating some patients with severe AA with mild side effects [20]. Results of another study comparing the efficacy of high-dose corticosteroid pulse therapy and combination therapy of cyclosporine plus low-dose corticosteroid in severe AA revealed that patients who received a high dose of intravenous methylprednisolone experienced more than 50% improvement during six months of follow-up. Notably, 20%–26% relapse occurred in both groups without any significant difference. A profound positive correlation between a recent disease onset and a desirable response was seen, such that 85% of patients with a disease onset of fewer than three months showed significant hair regrowth. Among all types of severe alopecia, plurifocal AA showed a better improvement than any other kind. This study indicated that intravenous methylprednisolone pulse therapy was a better treatment option than combination therapy with low-dose methylprednisolone and cyclosporine in patients with severe, plurifocal AA [21].

Intravenous Methylprednisolone Combined With Methotrexate

Droitcourt et al evaluated the efficacy of combining intravenous methylprednisolone pulse with methotrexate in treating multifocal AA. More than half of the patients experienced completed hair growth, while the rest had satisfactory incomplete responses. The mean period of hair regrowth initiation was 2.5 months, and relapse occurred in a few patients. The study concluded that this combination is effective and well-tolerated when treating patients with severe AA [22].

The Efficacy of Oral Corticosteroid Pulse in Treating Severe AA

Fourteen studies evaluated oral steroid pulse therapy in treating severe AA, including 2 on methylprednisolone, 3 on dexamethasone, 5 on prednisolone, and 4 studies on betamethasone.

Oral Methylprednisolone

Two studies assessed methylprednisolone pulse efficacy in AA treatment: one evaluated oral mega-pulse efficacy, relapse, and side effects, while the other evaluated oral mini-pulse. Saif et al prescribed an oral mega-pulse of methylprednisolone for 24 weeks with different protocols, namely three consecutive days once every two weeks, two consecutive daily pulses every three weeks, and three consecutive daily pulses every three weeks. No significant difference was seen between the groups in efficacy, and all

protocols induced a desirable response rate, as more than 50% of patients experienced more than 25% improvement in hair growth during treatment. Early age of disease onset, hypothyroidism, and longer duration of AA (more than two years) were associated with lower response. There was a significant difference in the side effects rate between the study groups, as patients who received steroid pulse with higher doses and shorter intervals experienced greater and more severe complications like arthralgia, increased appetite, and stomach upset. This study suggests oral mega pulse methylprednisolone as an effective choice for treating severe AA, albeit with a high risk of adverse events and a high relapse rate [23].

In another study by Thi et al, patients were treated with an oral mini-pulse of methylprednisolone, 16 mg/day, for two consecutive days per week. More than 82% of patients had good regrowth over six months, while only 40% had the same experience within three months. They suggested the mini-pulse of methylprednisolone as a safe and effective treatment for AA in six months [24].

Oral Dexamethasone

Among all articles, three were evaluated for dexamethasone pulse therapy effect in AA treatment: two evaluated the oral mini-pulse, and one assessed the combination of oral pulse with topical corticosteroids.

Oral Mini-pulse of Dexamethasone

Sánchez-Díaz described 40 patients with extensive scalp AA treated with dexamethasone oral mini-pulse (mean dose of 2.7 mg/day, two days weekly, 12 months). Higher effectiveness was reported as the treatment period increased. Oral dexamethasone pulse was relatively ineffective in patients with hypothyroidism and those aged under 15 years. No greater reduction in the Severity of Alopecia Tool (SALT) score was reported in combination therapy of dexamethasone pulse and oral minoxidil (25). Another study by Sharma et al. on 30 patients with widespread and diffuse AA who received oral dexamethasone showed promising results, as more than 60% of patients had completed or over 75% hair growth during five months. Relapse was uncommon as it was seen only in one patient. Frequent but mild and transient side effects were reported [26].

Oral Mini-pulse of Dexamethasone Combined With Topical Corticosteroids

Lalosevic et al studied 65 individuals aged 8–12 years with AA, alopecia universalis, and plurifocal AA. Oral pulse dexamethasone (once every four weeks) was combined with topical clobetasol 0.05% ointment to treat patients for 6–12 months. Almost 60% of patients had hair regrowth of more than 50% (most had >75% regrowth). The most satisfactory results were seen in patients with plurifocal AA. Patients with a disease duration of more than 12 months needed longer treatments. No serious adverse effects were reported [27].

Prednisolone

Four studies focused on the effect of prednisone pulse in treating severe AA. Among all, 3 articles studied high doses of prednisolone pulse, one study evaluated the possible pathway of the effect of prednisolone in treating AA by examining serum and tissue tumor necrosis factor-alpha (TNF-α) levels, and one compared the efficacy of oral prednisolone, dexamethasone, and intramuscular triamcinolone.

Oral High-dose Prednisolone Pulse

To assess the efficacy of the oral prednisolone pulse, Sharma et al enrolled 32 patients with more than 40% scalp involvement or persistent AA and treated them with a 300 mg monthly dose of prednisolone pulse. More than half of the patients had an excellent response. Patients with plurifocal alopecia areata had the most desirable cosmetic effects, while no improvement was seen in patients with alopecia universalis. Patients with alopecia universalis and non-responders to the 300 mg prednisolone pulse were retreated with a 1000 mg prednisolone pulse; nearly 50% regrowth was seen in this group during the follow-ups. Results showed that the 300 mg prednisolone pulse was an effective treatment for plurifocal alopecia areata with mild side effects, while the 1000 mg prednisolone pulse might be an effective choice in alopecia universalis and widespread resistant AA. The female gender, disease duration of over two years, and alopecia universalis were linked with a poor or lack of response to treatment [28].

A placebo-controlled study in a total of 43 patients revealed that 35% of the patients who received prednisolone pulse experienced significant hair growth at the end of three months. However, relapse occurred in 25% of them during the three months of follow-up. Patients with early age of onset, disease duration of fewer than two years, and those on their first episode responded better compared to those with atopy-related, nail involvement, multiple episodes, and prolonged duration. Mild side effects of corticosteroids were seen in 55% of the patients. However, they all eased gradually during the follow-up period]. Another study by Tsai et al tested high-dose steroid pulse therapy, 5 mg/kg oral prednisone in individuals under 12, and 500 mg intravenous methylprednisolone in adults with severe AA. Within four months of treatment initiation, favorable results were achieved, as all patients with multifocal AA experienced significant regrowth. However, the treatment outcomes were worse in patients with alopecia ophiasis, alopecia universalis, alopecia totalis, and extended disease lasting more than

two years. This study suggested monthly corticosteroid pulse therapy with a mean dose of 5-10 mg/kg as an effective treatment for severe multifocal AA lasting less than two years, with a low relapse rate [30].

Prednisolone Possible Mechanism of Action in AA

To assess the possible mechanism of action of prednisolone in the treatment of AA, Abdel Halim et al compared tissue and serum levels of TNF-α in 20 patients with AA and 20 controls. This study indicated that the disease duration significantly decreased after consuming 60 mg of prednisolone twice weekly for three months. There was a positive relationship between TNF-α level and AA lesions. Both serum and tissue levels of TNF-α were higher in the pretreatment evaluations of patients compared to the control group. Post-treatment assessments revealed a statistically significant decrease in patients' serum and tissue levels of TNF-α. They suggested the prednisolone pulse as a good choice for the treatment of AA, as it reduced the disease duration and TNF-α levels [31].

Comparison of the Efficacy of Oral Prednisolone, Dexamethasone, and Intramuscular Triamcinolone

A study published in 2006 by Kurosawa et al compared the efficacy, relapse rate, and side effects between three modalities of systemic corticosteroid therapy (oral prednisolone, dexamethasone, and intramuscular triamcinolone) in 89 patients with AA. In most patients, hair growth was evident 3-6 months after the first treatment session. According to the results, the overall response rate was significantly different only between the dexamethasone group and the intramuscular triamcinolone group patients in each clinical subtype (mostly in multiplex AA). To conclude, both prednisolone pulse therapy and intramuscular triamcinolone are effective treatments for AA with mild side effects. However, overall relapse rates were significantly higher in the dexamethasone group than in the prednisolone group (especially for those with alopecia totalis and alopecia universalis). The authors concluded that new strategies are needed to reduce relapse rates [32].

Betamethasone

Four studies were done on betamethasone efficacy in severe AA. One assessed mini-pulse of betamethasone, one compared azathioprine pulse with betamethasone, one assessed combination therapy of betamethasone and methotrexate, and the other examined a combination of betamethasone mini-pulse and topical minoxidil and anthralin.

Oral Mini-pulse of Betamethasone

One study evaluated the efficacy of betamethasone oral mini-pulse therapy in patients with severe AA. According to the results, most patients (74.9%) showed an excellent or good response. There was, however, a relapse in one patient two months after stopping therapy. Only a few patients showed an unsatisfactory or lack of response at the end of the six months of therapy. Both non-responders had alopecia universalis. They concluded that betamethasone is a safe and effective treatment for extensive AA, with only mild, reversible side effects [33].

To compare the efficacy of betamethasone oral mini-pulse versus weekly azathioprine pulse in treating scalp alopecia, Gupta et al. enrolled 50 patients into two groups of 25. Assessments of the results at baseline and after four and nine months demonstrated that both methods were highly effective options in treating severe alopecia with no priority, as almost 60% of patients in each group experienced complete regrowth within the nine months. However, betamethasone consumption was accompanied by some severe side effects. They suggested azathioprine pulse as a good and safe alternative to steroid therapy in severe alopecia with minor side effects [34].

Combination of Oral Mini-pulse of Betamethasone With Other Agents

Asilian et al compared 36 patients treated with either betamethasone 3 mg/once a week, methotrexate 15 mg/once a week, or a combination of them for four months. Patients in all groups experienced a significant increase in hair regrowth; however, greater regrowth was seen in patients treated with betamethasone and combination therapy compared with methotrexate alone. Among all, combination therapy was the most effective, especially in the long-term period of consumption of the drugs [35].

In 2011, Deshpande et al. proposed a combination therapy in which the patients were treated with oral betamethasone mini-pulse (0.1 mg/kg twice a week) along with topical minoxidil and anthralin cream of 2%-5% and 1.15%, respectively. Topical minoxidil was applied to the affected area twice, 12 hours apart. The anthralin cream was first applied at night, two hours apart from the minoxidil application, for 10 minutes (contact time), then the contact time gradually increased every three weeks until mild erythema appeared. There was a high response rate (80%) among the patients. The response rate was low among the patients with alopecia universalis or prolonged alopecia totalis, while all patients with ophiasis and severe AA showed cosmetic improvements. Due to the synergistic interactions between the drugs, this combination therapy could be used as an effective and safe treatment for patients with treatment-resistant and extensive alopecia areata [36].

Conclusions

Alopecia areata (AA) is a common, non-scarring, autoimmune hair loss disorder. It is a multifactorial disease that varies in clinical presentation from a small patch to total

scalp and body alopecia. Finding the appropriate treatment protocols for AA is challenging due to the disease's uncertain pathogenesis and unpredictable remission rates (6). The use of systemic pulse corticosteroids was first introduced for treating severe types of AA in 1975 by Burton and Shuster to decrease possible side effects of long-term use of corticosteroids and increase the effectiveness of the treatment. They treated 22 patients with a single intravenous dose of methylprednisolone, but only 23% responded. The unsuccessful results were due to poor patient selection, as most patients had severe AA for a long time [10]. Afterward, several scientists followed them and administered pulse steroid therapy in various forms and doses with or without other drugs to avoid the long-term side effects of prolonged steroid therapy. In this study, we considered 24 published studies and reviewed their modalities for treating different kinds of AA.

A review of the studies on the efficacy and side effects of intravenous methylprednisolone revealed that pulse therapy of methylprednisolone might be a promising treatment option in the severe form of AA with the routine treatment protocol of 8-10 mg/kg for three consecutive days, with one-month interval up until the clinical satisfaction achieve, either for adults or children. There is no difference in the outcomes and side effects of the routes of choice (intravenous or oral). The relapse rate and efficacy depend on the time of AA onset, patient age, and the type of AA; recent onset of AA (<6 months), younger age (<10 y/o), and multifocal type of AA (compared to alopecia universalis, totalis, and ophiasis) are linked with better results and a lower chance of relapse. Patients with a past medical history of atopy, nail pitting, or thyroid disease and those with severe forms of AA like alopecia universalis and totalis experienced less improvement [13-19].

A combination of intravenous pulse methylprednisolone with methotrexate (12.5 mg weekly) revealed the best efficacy for treating the severe type of AA, although some poor prognostic factors such as childhood onset of the disease, disease duration >6 years, and a positive history of atopy or nail pitting led to poor outcomes and increase the risk of relapse. The use of sequential intravenous pulse therapy of methylprednisolone is supposed to be better than a single dose to decrease the risk of relapse. Studies on the effect of combination therapy with cyclosporine are still controversial, but some articles have shown promising results [20-22].

Research on the efficacy of oral methylprednisolone pulse therapy showed that both oral mega-pulse and mini-pulse of methylprednisolone are effective in severe forms of AA, but the relapse rate is high. There is a significant difference in relapse rate and adverse effects, as the mini-pulse of oral methylprednisolone is safer; higher doses and shorter intervals lead to greater and more severe complications [23,24].

Studies proposed dexamethasone as a good treatment option for AA with a low rate of relapse and side effects. They also revealed no difference between the efficacy of oral mini-pulse dexamethasone (2.7 mg/day) vs. 5 mg/day for two days a week, so it's safer to use the lower dosage. To achieve better results in children, dexamethasone can be combined with topical clobetasol [25-27].

In the studies on betamethasone, excellent therapeutic responses can be achieved with a low relapse rate and only mild reversible side effects. Monotherapy with betamethasone mini-pulse (0.1 mg/kg/ day to 5 mg/day for 2consecutive days a week for a mean time of 6 months) is accompanied by highly successful results but some adverse effects, while combination therapy of betamethasone with methotrexate or topical minoxidil and anthralin significantly increase hair regrowth and decrease the side effects [33-36].

Articles focused on the efficacy of prednisone pulse therapy have found prednisolone (5-10 mg/kg/month for 4-6 months) as an acceptable and effective option with a low relapse rate. Results showed that an average dose of 300 mg monthly prednisolone pulse is an effective treatment for plurifocal AA with only mild side effects, but patients with alopecia universalis or alopecia totalis are resistant to this therapy. Research suggests 1000 mg prednisolone is an effective choice in alopecia universalis and resistant widespread alopecia areata [28-30].

Comparisons of the efficacy of oral dexamethasone, oral prednisolone, and intramuscular triamcinolone revealed that all methods are effective, but the best results were achieved with intramuscular triamcinolone, followed by prednisolone, with only mild reversible side effects. Patients who received dexamethasone experienced less hair regrowth with a higher relapse rate [32].

In conclusion, all mentioned systemic corticosteroid pulses effectively induce hair regrowth in alopecia areata. Both forms of intravenous and oral corticosteroids have acceptable efficacy. Betamethasone pulse seems to be the most effective agent in the treatment of AA (followed by intramuscular triamcinolone), especially in severe cases, but more side effects may accompany it. Combining this agent with other medications can reduce the dosage and side effects. Prednisolone and methylprednisolone pulse are less effective but safer options, with low relapse rates and few adverse effects. A combination of them with other drugs can increase their efficacy.

Reference No.	Title	First author	Trial type	Year	Patients (No., sex)	Age (y)	Alopecia type	Treatment	Assessment	Outcome	Conclusion	Side effects
1	Pulsed administration of corticosteroids in the treatment of alopecia areata	Sharma, VK	Prospective	1996	32: 24M, 8F	14–48 (mean 28.5)	Widespread alopecia, AT, AU	A: 300 mg oral prednisolone monthly for a minimum of 4 doses or until cosmetically acceptable hair growth was obtained; B: 1000 mg prednisolone	Monthly evaluation and serial photographs; the results were listed at 6 and 12 months by measuring the percent of terminal hair growth.	A: 58.3% had complete or 80–95% hair growth. B: 3 out of 7 had cosmetically acceptable growth. In general, women and patients with alopecia for more than two years or AT or AU showed poor or no response.	Effective treatment for widespread alopecia areata with only mild side effects	A: A man experienced nausea; a woman got polymenorrhea. B: No side effects
2	Pulse methylprednisolone therapy for severe alopecia areata: an open prospective study of 45 patients	A. Friedli	Open, prospective	1998	45	13–66	PF AA, OA, AU, and AT	250 mg IV methylprednisolone, twice a day on 3 consecutive days	Two independent observers measured the percentage of hair regrowth at 1, 3, 6, and 12m. Serial photographs and monthly examinations were done.	Patients with multifocal AA showed the best response, while patients with OA, AU, and AT did not respond well. Relapse occurred in 10 in 7m; after a year of follow-up, only 12 were still in remission.	Effective treatment in patients with multifocal AA, but not in those with AU, AT, or OA	Only common mild transient side effects of steroids: fatigue, nausea, dyspnea, palpitation, and headache
3	Twice weekly 5 mg dexamethasone oral pulse in the treatment of extensive alopecia areata	Sharma VK	Prospective	1999	30: 20M, 10F	6–46 (mean 23.6)	Extensive alopecia and circumscribed alopecia	5 mg dexamethasone orally, twice weekly for 6m or until acceptable hair growth	Monthly examinations were done, and the results were reported at 6 and 12 months as complete (100%), excellent (75-95%), good (51-74%), or poor (<50%) hair growth.	After 5.35 months, hair growth was complete or excellent in 19 patients, good in 2, poor in 3, and absent in 6.	Effective modality in treating severe multifocal alopecia with only mild common side effects.	Commonly mild side effects of corticosteroids were seen in 8 patients; in only one patient, the treatment had to stop due to the side effects.

Reference No.	Title	First author	Trial type	Year	Patients (No., sex)	Age (y)	Alopecia type	Treatment	Assessment	Outcome	Conclusion	Side effects
4	High-dose steroid pulse therapy for the treatment of severe alopecia areata	Ya-Ming Tsai	Prospective	2002	17: 8M, 9F	8–53 (mean 25)	Multifocal AA, OA, AU, and AT	Children <12: 5 mg/kg oral prednisone in three divided doses monthly; Adults: monthly 500 mg IV methylprednisolone infusion over two hours (for a maximum of 6 months)	Serial photographs were taken, and two blinded dermatologists evaluated hair growth. The average of the results was tabulated. A satisfactory response was defined as more than 75% hair regrowth.	11 patients with multifocal AA showed partial hair growth, while 2 showed no response. Less effective in OA, AT, AU, and extended AA.	Effective modality in treating severe multifocal AA lasting less than two years	
5	Placebo-controlled oral pulse prednisolone therapy in alopecia areata	Bikash Ranjan Kar	Placebo-controlled	2005	Group A: 20: 14M, 6F Group B: 16: 12M, 4F	Group A: 26.3 ± 7.3. Group B: 30.2 ± 10.2	Severe AA	Group A: 200 mg of oral prednisolone weekly for 3m; Group B: matched placebo tablets on an identical schedule	Patients were examined monthly for marked (>60%), moderate (31–60%), or poor (<30%) regrowth.	A: 8 had significant hair growth after 3m (2= marked, 6= moderate), though 2 later relapsed. Poor response: atopy-related AA, nail involvement, multiple episodes, & extended AA B: None responded.	This therapy is effective and promising, but more research needs to be done to adjust the dose needed.	Mild frequent side effects of corticosteroids were seen in 55% of the patients. However, they all eased gradually during the follow-up period.

6	A comparison of the efficacy, relapse rate and side effects among three modalities of systemic corticosteroid therapy for alopecia areata	Masahiro Kurosawa	Randomized comparative-prospective study	2006	89	16-63 years	PF AA, AT, AU	Dex group (n=19): oral Dex 0.5 mg/day for 6m; IM triamcinolone acetonide (imTA) group (n=43): imTA 40 mg monthly for 6m followed by 40 mg once every 1.5 months for 1 year; PT group (n=29): oral prednisone 80 mg for 3 consecutive days every 3m	The response was tabulated monthly by measuring the percentage of terminal hair growth. Serial photographs were taken at baseline and after 3, 6, and 12m.	In most patients, hair growth was evident at 3–6m. The overall response rate was significantly different only between the Dex and imTA groups, in each clinical subtype (mostly in multiplex AA).	Both imTA and pulse therapy are effective for AA with only mild side effects. A high relapse rate (especially in AT and AU) was seen in the Dex group.	10% of PT group patients: dysmenorrhea and abdominal discomfort; 41% of imTA group patients: dysmenorrhea, abdominal discomfort, and worsening acne; 30% of Dex group patients: weight gain, abdominal discomfort, weakness, and mooning.
7	Extensive alopecia areata treated with betamethasone oral mini-pulse therapy: An open uncontrolled study	Binod K. Khaitan	Open, uncontrolled	2004	16: 11M, 5F	14–36 (mean 26)	Severe AA	A single dose of 5 mg betamethasone was administered biweekly for at least 6m.	Monthly examinations to assess the treatment response and adverse effects; patients were followed up for 5–8m for relapse of the disease.	43.7% had an excellent response (relapse occurred in 1 patient after 2m). 31.2% showed a good response, and therapy was continued for another 2m in these patients (no relapse occurred). 4 patients showed poor or no response (non-responders had AU).	Effective therapeutic modality for extensive alopecia areata	Only mild side effects including moon face, acneiform eruption, weight gain, and abdomen discomfort

Reference No.	Title	First author	Trial type	Year	Patients (No., sex)	Age (y)	Alopecia type	Treatment	Assessment	Outcome	Conclusion	Side effects
8	Extensive alopecia areata: not necessarily recalcitrant to therapy!	Deepal Deshpande	Prospective	2011	15: 10F, 5M	7–45	Extensive AA	Oral betamethasone mini-pulse (0.1 mg/kg twice a week) along with 2–5% topical minoxidil (twice a day, 12 hours apart) and 1.15% anthralin cream (daily). After achieving a response, the oral steroid was tapered step-wise and then stopped, but the topical creams were continued as maintenance therapy and then gradually decreased.	Monthly evaluation by measuring the percent of terminal hair growth. Cosmetic response: partial dense patches of terminal hair, obviating the need for a wig/cap; non-responders or failure: no growth or vellus hair.	80% responded. Among the 20% non-responders, 2 had AU and one had extended AA with a duration of 8–10 years. Out of 8 patients with AU/AT: cosmetic response=4, partial response=1. Cosmetic response was seen in all 4 patients with OA and all 3 patients with severe AA.	This combination therapy is an effective and safe treatment for patients with treatment-resistant and extensive AA.	Only mild, reversible side effects
9	Efficacy and safety of oral mega pulse methylprednisolone for severe therapy resistant alopecia areata	Ghada A	Prospective randomized	2012	42: 20F, 22M	12 ± 7	AU, AT, OA	Group 1: 15 mg/kg MP, 3 days every 2w for 24w; Group 2: 15 mg/kg MP, 2 days every 3w for 24w; Group 3: 15 mg/kg MP, 3 days every 3w for 24w	Photography at baseline and every 2w. >75% regrowth: adequate; 25-75%: inadequate. <25%: poor	Nearly 30% had an adequate response, 20% inadequate, and 50% poor response at 36w; no difference between the groups. Older age of initiation had a better response.	MP pulse therapy is relatively effective in severe AA but has a high relapse rate	95% experienced side effects. Fatigue: 64%; weight gain: 45%; steroid-induced acne: 35.7%; sleep disturbances 33%. Others: irritability, lethargy, stomach upset, nausea, flushing, cramp, bony pain, arthralgia

10	Combined oral pulse and topical corticosteroid therapy for severe alopecia areata in children: a long-term follow-up study	Jovan Lalosevic	Retrospective	2015	65	10 ± 5	>30% scalp involvement AU, AT, PF AA	Oral dexamethasone (equal to 5 mg/kg prednisolone) once every 4w (6, 9, or 12 pulses) plus topical clobetasol, 6 days a week.	According to the AA investigational assessment guidelines, photos were evaluated by a board-certified dermatologist at baseline, 3, 6, 9, and 12m.	83% with PF AA had regrowth >75%, while 35% with severe AA had the same experience. Relapse: 16.9%	Combined topical and oral corticosteroid pulse is effective for severe AA in children without any severe side effects	No serious side effects
11	Alteration of serum and tissue tumor necrosis factor alpha levels: A possible mechanism of action of oral pulse steroids in the treatment of alopecia areata	Dalia Abdel Halim	Prospective	2018	40	28 ± 11	PF AA	Group 1: 60 mg/day of prednisolone, biweekly for 3m (age <16 received half dose); Group 2: Control	3-ml blood sample and 2-mm punch biopsy were assessed for TNF-α level before and after treatment	Serum and tissue TNF-α levels significantly decreased after the treatment.	Prednisolone pulse is a good choice for treating AA as it reduces the disease duration and TNF-α level	
12	The effectiveness of oral mini-pulse methylprednisolone in the treatment of alopecia areata in Vietnam	Phuong Trinh Thi	Prospective	2019	45	>16	Not mentioned	Oral mini-pulse MP 16 mg/day biweekly for 6m	Not mentioned	40% had regrowth by 3m, and 82% had regrowth by 6m	Oral mini-pulse of MP is an effective, safe, and low-priced treatment for AA	No side effects
13	Weekly azathioprine pulse versus betamethasone oral mini-pulse in the treatment of moderate-to-severe alopecia areata	Prashant Gupta	Open-label, randomized comparative	2022	50	25	>10% scalp involvement	Group 1: 300 mg weekly azathioprine (WAP) for 4m; Group 2: 5 mg betamethasone biweekly for 4m	SALT score; average percentage of scalp hair regrowth; evaluations at baseline and 4 & 9m	44% regrowth in the WAP group and 71% in the betamethasone group; 50% in WAP and 62% in betamethasone group had complete hair growth at 9m	WAP and oral-mini-pulse of betamethasone are both effective in treating AA, with no priority in hair growth, though betamethasone pulse has more side effects	Moon face, acne, reflux, and weight gain were seen in steroid group, while only transient nausea was reported with WAP

Reference No.	Title	First author	Trial type	Year	Patients (No., sex)	Age (y)	Alopecia type	Treatment	Assessment	Outcome	Conclusion	Side effects
14	Oral pulse betamethasone, methotrexate, and combination therapy to treat severe alopecia areata: a randomized, double-blind, placebo-controlled, clinical trial	Ali Asilian	Randomized, double-blind, placebo-controlled	2020	36	27	>50% scalp involvement	Group 1: 3 mg betamethasone weekly for 6m; Group 2: 15 mg MTX weekly for 6m; Group 3: 3 mg betamethasone+15 mg MTX weekly for 6m	SALT, VAS, & photography at baseline and 3, 6, & 9m	Significant improvement in SALT, VAS, and photographic scores in all at 3, 6, & 9m; At 9m: a 43% SALT score decrease in Group 3, 26% in Group 1, and 23% in Group 2, & Group 3 showed significantly more VAS/ photographic scores improvement	MTX & betamethasone alone or in combination are effective in treating severe AA, though betamethasone or betamethasone + MTX are more effective than MTX alone	1 patient in MTX group and 1 in combination group developed gastrointestinal symptoms, relieved with daily folic acid
15	Alopecia areata and dexamethasone mini-pulse therapy, a prospective cohort: real world evidence and factors related to successful response	Manuel Sánchez-Díaz	Prospective cohort	2022	40	32	>20% SALT score	Oral Dex at a mean dose of 2.72 mg/day biweekly for 12m; 27% of patients received oral minoxidil 0.5-1 mg/day for females, 2.5-5 mg/day for males	SALT at baseline, 3, 6, 9, 12m	50% decrease in SALT score in half the patients by 9m. Significant decrease in SALT score in overall assessment. No SALT score decrease in onset age < 15y	Oral mini-pulse of Dex is effective in treating AA but ineffective for onset age <15y or in those with hypothyroidism	Weight gain in 35%; osteopenia or osteoporosis in 12.5%; glycemic disorder in 5%; acneiform rash, hirsutism, anxiety, and insomnia in less than 5%
16	The effect of methylprednisolone pulse-therapy plus oral cyclosporine in the treatment of alopecia totalis and universalis	Mohammad Shaheedi-Dadras	Prospective	2008	18: 9F, 9M	20.6 ±4.8 (range14–29)	AT, AU	500 mg dose of IV MP monthly for three days + oral cyclosporine (2.5 mg/kg/day) for 5–8m.	Adequate= hair regrowth ≥70% and inadequate= regrowth <70%.	Total of 6 patients showed adequate response= 33% (3M and 3F/ 3 in patients<20y and 3 in patients>20y/ 2 with a history of atopy, 3/6 with AT and 3/12 with AU)	This therapy can be beneficial in some patients with resistant and severe AA.	Mild hypertension (n=1), hyperlipidemia (n=2), and mild acne (n=1)

Reference No.	Title	First author	Trial type	Year	Patients (No., sex)	Age (y)	Alopecia type	Treatment	Assessment	Outcome	Conclusion	Side effects
17	Early intervention with high-dose steroid pulse therapy prolongs disease-free interval of severe alopecia areata: a retrospective study	Chao-Chun Yang	Retrospective	2013	85: 39M, 46F	28.4 (range4–60)	AT, AU, AO; alopecia >50%	2.5–10 mg/kg/day of oral prednisolone or IV MP for 3 consecutive days	Photography at baseline and end of treatment; satisfactory response: hair regrowth more than 75%; scoring based on the Alopecia Areata Investigational Assessment Guidelines	>75% regrowth in 51% of patients. More satisfactory results in 50-70% baldness rather than AU or AT; better response when treated during 1st year of disease	IV and oral pulse of steroids are safe options in treating severe AA, showing equal efficacy; initiation time plays an important role in the efficacy rate	Mild and transient side effects in both groups: flushing, hyperglycemia, increased appetite, insomnia, & palpitations; no long-term side effect
18	Pulse corticosteroid therapy for alopecia areata: long-term outcome after 10 years	D. Staumont-Sallé	Retrospective	2012	30: 10M, 20F	27.4 (range5–63)	AT, AU, AO, PF AA, and 30–50% AA	500 mg–1 gr (or 10–20 mg/kg) IV MP for 3 consecutive days/m for 3m	Phone interviews; online supplementary questionnaire (www. karger.com/doi/10.1159/000341523); clinical examinations; DLQI; all were done 10 years after treatment	More than half still had severe AA; those with initial response to therapy during first 6m had milder disease in next 10y vs. non-responders	Poor long-term efficacy of corticosteroid pulse in severe AA; recommended other kinds of treatment for this group of patients	22 out of 30 experienced side effects: tiredness, headache, flushing, nausea and vomiting, and transient hyperglycemia
19	Pulse corticosteroid therapy for alopecia areata in children: a retrospective study	Rivka Friedland	Retrospective study	2013	24: 8M, 16F	8 ± 4.6	AT, AU, AO, PF AA	8–10 mg/kg IV MP for 3 consecutive days, monthly	Monthly clinical examination	38% complete response, 29% partial response, 33% no response, 81% relapse; Good prognostic factors: age <10y & disease initiation <6m	MP pulse is effective in children with PF AA, with a high relapse rate but minimal side effects	Only 3 patients had very mild transient side effects

Reference No.	Title	First author	Trial type	Year	Patients (No., sex)	Age (y)	Alopecia type	Treatment	Assessment	Outcome	Conclusion	Side effects
20	Comparison of high-dose corticosteroid pulse therapy and combination therapy using oral cyclosporine with low-dose corticosteroid in severe alopecia areata	In Kwon Yeo	Retrospective	2015	142: 79M, 63F	8~80 years (mean, 35.1 years)	PF AA, AT, AU	Group A: IV-pump MP 1 g/day, twice a day for 3 consecutive days for adults and 10 mg/kg/ day weekly for 3w for children + oral MP 30 mg/day for 3 days;Group B: oral cyclosporine (2.5 mg/kg/day + MP (2.5–5 mg/day) for 4m	Hair regrowth was evaluated on a scale of 0-100%. Good response: regrowth of >50% of the lesion surface	Good response rate was higher in Group A. Patients in Group A with PF AA and those with disease duration ≤3m had better response, whereas in Group B, the disease duration/type did not affect the response. PF = better response than the others.	Pulse corticosteroid therapy is a better treatment option than combination therapy in patients with severe AA and PF AA	Group A: gastrointestinal discomfort, headache, dizziness, facial flushing, and palpitation; Group B: gastrointestinal discomfort, headache, and hypertension
21	Pulse corticosteroid therapy for alopecia areata: study of 139 patients	Takeshi Nakajima	Retrospective	2007	139: 43M, 96F	15–73 (mean age: 35.1)	Recent-onset extensive AA	500 mg IV MP over an hour on 3 consecutive days	Evaluation of hair regrowth was made mostly by the attending investigators (84.2%) and by serial photos after 6m	Recent-onset disease linked with more regrowth; patients with recent-onset and less severe disease (<50%) responded better than patients with recent-onset and 100% hair loss; none of the patients with 100% hair loss and >6m of AA history responded; relapse in 16.7% of good responders (n=66) during 15.3m mean follow-up	This therapy is effective and promising in patients with less severe AA (<50%) and in patients with recent-onset of AA, with only mild adverse effects of corticosteroids	Only mild & transient side effects: palpitations, headache, low-grade fever, and insomnia

22	Multiple courses of pulse corticosteroid therapy for alopecia areata	Takashi Yoshimasu		2016	55:13M, 41F	16-64	AA	IV MP 500 mg/day was infused over 2 h on 3 consecutive days (at least one course of therapy up to three courses)	The development of vellus hair: good response to short-term therapy; good long-term response (6m after the last pulse): >75% hair regrowth on alopecia lesions	Fewer courses of PT required for vellus hair to develop in patients with <50% hair loss and <6m disease onset; good short-term and long-term response rate (100%) in patients with <50% hair loss regardless of disease duration; no response in those with 100% hair loss for >6m	This treatment can be considered an effective modality in treating recent-onset severe AA and in patients with less extensive disease	Transient mild side effects in 5 patients: muscular pain in extremities, finger numbness, leg edema, and stomach discomfort; treatment was stopped
23	High-dose pulse corticosteroid therapy in the treatment of severe alopecia areata	Simone Seiter	Monocenter, prospective	2000	30	14–56 (mean 31)	PF AA, OA, AT, AU	IV MP (8 mg/kg body weight) over 30 min on 3 consecutive days at monthly intervals	Re-examination at 1, 3, 6, & 12m after completion of a 3-course treatment; serial photographs compared with the pretreatment status by 2 independent investigators	40% of the patients had >50% regrowth and 13% had 10-50% regrowth; 67% of patients with PF AA had >50% hair growth, while none with OA/AT/AU showed >50% hair growth	IV MP is a safe and effective treatment option for PF AA, while it is less effective in patients with AT, AU, or OA	Transient mild side effects included headache (n = 5), fatigue (n = 3), palpitations (n = 2), and nausea (n = 1).
24	Interest of high-dose pulse corticosteroid therapy combined with methotrexate for severe alopecia areata: a retrospective case series	Catherine Droitcourta	Retrospective case series	2012	20: 12F, 8M	14–57 (mean 33)	Multifocal AA, AT	500 mg dose of IV MP in 3 consecutive doses monthly for at least 3m in combination with MTX (12.5 mg/week up to 25 mg/week over the next 6m) at the end of the second pulse regimen	Monthly assessments during the first 3m of treatment, and then every 3m by a dermatologist; serial photographs were taken during visits; hair growth was evaluated on a scale of 0–100%	The mean period of hair regrowth initiation was 2.5m. By 18m, multifocal AA responded better than AT. Patients with >12m disease duration responded more vs. patients with <12m	This treatment can be considered effective and well tolerated in treating severe AA, though a longer follow-up is recommended.	No side effects of corticosteroids were recorded. Only 3 patients had MTX-related side effects (nausea in 2 and neutropenia in 1) and stopped treatment after 5 months.

AA = Alopecia Areata; AT = Alopecia Totalis; AU = Alopecia Universalis; F = Female; IM = Intramuscular; IV = Intravenous; M = Male; m = months; MP = Methylprednisolone; MTX = Methotrexate; w = weeks; OA = Ophiasis Alopecia; PF = Plurifocal; PT = Pulse Therapy; TNF-α = Tumor Necrosis Factor-alpha; WAP = Weekly Azathioprine; SALT = Severity Alopecia Tool; VAS = Visual Analogue Scale; Dex = Dexamethasone; DLQI = Dermatology Life Quality Index.

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