

Hair Loss Induced by Tumor Necrosis Factor Alpha Inhibitors

Keywords: Tumor necrosis factor alpha inhibitors; Etanercept; Adalimumab; Infliximab; Alopecia; Alopecia areata; Psoriatic alopecia; Lichen planopilaris; Adverse reaction

Abstract

Background: Alopecia is a possible adverse reaction to Tumor Necrosis Factor alpha (TNF- α) inhibitors. This side effect has become more recognized in recent years through FDA postmarketing surveillance and its description in case reports/case series.

Objective: We review the literature and summarize the pathogenesis, clinical presentation, prognosis, and management strategies for TNF- α inhibitor induced alopecia.

Methods: We performed a Medline search from January 1998 until August 2013 to identify all cases of alopecia during anti-TNF- α therapy described in the literature. We also reviewed FDA postmarketing data and clinical trials.

Results: There were 62 cases of hair loss occurring during therapy with TNF- α inhibitors that we identified during our literature search. The causes of hair loss included alopecia areata, psoriatic alopecia, lichen planopilaris, drug-induced lupus erythematosus, androgenetic alopecia, and telogen effluvium. Alopecia was also a mentioned side effect in three clinical trials and in FDA postmarketing surveillance.

Limitations: There are few controlled trials directly studying TNF- α inhibitor induced alopecia and most of our understanding of this clinical condition comes from anecdotal experience.

Conclusions: TNF- α inhibitors can cause different types of hair loss including severe alopecia areata and scarring alopecia.

Abbreviations

TNF- α – Tumor Necrosis Factor Alpha; IL – Interleukin; IFN – Interferon; pDc – Plasmacytoid Predendritic Cells; LPP – Lichen Planopilaris; NSAID – Nonsteroidal Anti-Inflammatory Drug; DILE – Drug-Induced Lupus Erythematosus

Introduction

Tumor necrosis factor alpha (TNF- α) inhibitors comprise a specific class of biologic drugs that has become increasingly common, especially in dermatology. This class of medication is currently FDA approved for the treatment of Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and juvenile idiopathic arthritis [1-3]. Through their off-label use, they have been shown to be effective for the treatment of a wide range of other immune-mediated conditions as well [4].

There are three different tumor necrosis factor alpha inhibitors currently on the market: adalimumab, infliximab, and etanercept [1-3]. Adalimumab is a fully monoclonal human antibody [2] while infliximab is a chimeric mouse-human antibody [3]. These act by binding directly to both receptor-bound and freely circulating TNF- α molecules and neutralizing them [2,3]. Etanercept, on the other hand, is a TNF receptor-IgG fusion protein [1] and unlike adalimumab and infliximab, is unable to neutralize receptor bound TNF- α [5]. For this reason, adalimumab and infliximab are significantly more likely to induce apoptosis and cell lysis in inflammatory cells [5].



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Because of their ability to accurately act on specific targets in the body, biologic drugs such as TNF- α inhibitors were thought to have fewer side effects than other traditional systemic therapies such as methotrexate and cyclosporine. However, as their use has become more widespread, new side effects of TNF- α antagonists have been reported [6-8]. One side effect of TNF- α inhibitors is alopecia. This has become more evident in recent years through publications in the literature and FDA postmarketing surveillance. One study reported that 3.3% of patients taking TNF- α inhibitors experience hair loss, and this can be an important reason for discontinuing therapy [9]. In this review, we will discuss the topic of TNF- α inhibitor induced alopecia and summarize the pathogenesis, clinical presentation, prognosis, and management strategies for the different causes of this condition.

Materials and Methods

A Medline search from January 1998 until August 2013 was performed to identify the cases described in the literature of hair loss occurring during anti TNF- α therapy. The terms used in Medline were (alopecia OR alopecia areata OR psoriasis) AND (infliximab OR etanercept OR adalimumab OR anti-TNF-alpha). We included case reports, case series, review articles, and clinical trials which specifically mentioned hair loss occurring during treatment with TNF- α inhibitors. We included cases of alopecia which occurred in the treatment of diseases during both FDA approved and the off-label use of TNF- α antagonists. We also reviewed the drug package inserts and the FDA postmarketing data.

Results

Alopecia in Clinical trials

Although alopecia is an observed complication of anti TNF- α therapy, it is rarely studied directly in clinical trials and its true prevalence is therefore difficult to estimate. In two clinical trials of etanercept used to treat rheumatoid arthritis, alopecia was observed in six of 415 patients (1.45%) and one of 349 patients (0.29%) [1,10]. For infliximab, one study in patients with Crohn's disease reported that one of 100 (1.00%) patients developed alopecia [11]. The authors

were unable to find clinical trials directly measuring alopecia during treatment with adalimumab.

Alopecia in Postmarketing studies

Alopecia was found to be a relatively common side effect of anti TNF- α therapy in postmarketing studies [10,12]. It is listed as a potential adverse reaction in the package insert of Enbrel (etanercept) [1], Humira (adalimumab) [2], and Remicade (infliximab)[3]. Using eHealthMe to analyze data reported to the FDA [6-8], we attempted to estimate the prevalence of alopecia occurring with each TNF- α inhibitor. Alopecia was reported in 423 of the 79,722 (0.53%) people who reported side effects with infliximab [7], 1,495 of 166,330 (0.90%) patients with etanercept [6], and 1,291 of 130,505 (0.99%) patients with adalimumab [8]. It is important to note that this is self-reported information and these patients could be taking other agents which contribute to hair loss.

Alopecia in Case Reports/Case Series

In the literature, we discovered 62 cases of hair loss occurring during therapy with TNF- α inhibitors. The causes of hair loss included alopecia areata, psoriatic alopecia, lichen planopilaris, drug-induced lupus erythematosus, androgenetic alopecia, and telogen effluvium. The patients who developed anti TNF- α induced alopecia were being treated for a wide range of conditions which included psoriasis, psoriatic arthritis, Crohn’s disease, ulcerative colitis, Behçet’s disease, ankylosing spondylitis, rheumatoid arthritis, and idiopathic juvenile arthritis. There were 32 cases of alopecia described during treatment with adalimumab, 22 with infliximab, and nine with etanercept (in one case, both adalimumab and infliximab were used). By gender, there were 34 females, 25 males, and three unreported.

Clinical Subtypes of Alopecia Seen during Treatment with TNF- α Inhibitors

Alopecia Areata: Alopecia areata is a type of autoimmune-induced non-scarring alopecia with a calculated lifetime risk of 2% [13]. The pathogenesis is not fully elucidated but studies suggest pro-inflammatory cytokines such as IL-1 α , IL-1 β , and TNF- α play a major role in disease progression [14]. As such, one would expect TNF- α inhibitors to be effective treatment options for this condition. Not only have studies shown this not to be the case [15], alopecia areata has actually been found to occur during treatment with TNF- α inhibitors. The first case was reported in 2004 with the use of infliximab [16] and since then we have identified 34 cases in the literature, including the

TNF- α inhibitors adalimumab [4,17-27], infliximab [16,23,28-32], and etanercept (Table 1) [4,22,33,34]. In these cases, alopecia areata was diagnosed by both clinical presentation and histopathology, which was available in the majority of cases.

The clinical presentation of alopecia areata occurring during anti-TNF- α therapy can vary widely ranging from mild scalp patches to alopecia areata universalis [21]. The most common presentation is patchy alopecia involving the parietal and occipital regions [4]. Etanercept-induced alopecia areata appears to be less severe, as patients mostly exhibit solitary patches of hair loss. Alopecia areata occurring during treatment with adalimumab and infliximab has a more varied clinical presentation ranging from patchy hair loss to alopecia areata universalis and totalis, respectively (Table 1).

The average onset of symptoms was 9.9 months after the initiation of therapy, although presentation was documented to occur between 1 month and 3.5 years [4]. There were 15 males, 17 females, and two patients with unreported genders. The patients were being treated with TNF- α inhibitors for a wide range of conditions including psoriasis, psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, Crohn’s disease, and idiopathic juvenile arthritis. Most patients had no family or personal history of alopecia areata, although many suffered from other autoimmune conditions [4]. Interestingly, the occurrence of alopecia was noted to occur concurrently with other immune-mediated phenomena such as halo nevi [29] and psoriasisiform eruptions [34].

Patients with alopecia areata occurring during anti TNF- α therapy have a mixed prognosis, with approximately one third achieving complete hair regrowth while others continue to progress to alopecia areata universalis and totalis. All patients with alopecia areata occurring during treatment with etanercept showed improvement in symptoms, although none of these patients achieved full hair regrowth. Patients with alopecia areata development during treatment with adalimumab and infliximab had a more varied prognosis, ranging from full hair regrowth to progression to alopecia areata totalis.

There have been no clinical trials investigating the optimal treatment strategies for alopecia areata occurring during anti-TNF-therapy and most of our knowledge comes from anecdotal experience. The patients who achieved complete hair regrowth often did so after cessation of anti-TNF- α therapy although a minority of patients remained on the TNF- α inhibitor and still experienced some

Table 1: Alopecia Areata during Treatment with TNF- α Inhibitors.

TNF- α Inhibitor	Number of Cases	Time Lapse until Onset of Alopecia Areata (months)	Clinical Presentation	Prognosis
Adalimumab	20	1-24 (average 6.8)	Varied from patchy hair loss to alopecia areata universalis	Seven of 20 patients (35%) exhibited full hair regrowth; three patients remained stable without worsening or improvement of symptoms; two patients progressed to alopecia areata universalis and one progressed to alopecia areata totalis
Infliximab	8	1.5-24 (average 12.5)	Varied from patchy hair loss to alopecia areata totalis	All but one patient had at least a moderate degree of hair regrowth; five of eight patients (63%) had full hair regrowth; one patient progressed to alopecia areata totalis
Etanercept	6	2-42 (average 17.0)	Solitary patches on the scalp	All patients showed some improvement in symptoms although none demonstrated complete hair regrowth; no patients progressed to alopecia areata totalis or universalis.
Total	34	1-42 (average 9.9)		

hair regrowth [4,35]. There are currently no accepted guidelines governing whether the TNF- α antagonist should be discontinued in these situations, and this should be evaluated on a case-by-case basis. The application of topical steroids to the scalp was initiated in almost all patients, although it is unclear whether this provided an actual benefit. Nakagomi et al. described a patient who achieved hair regrowth only after the initiation of cyclosporine [28]. Methotrexate was also initiated in some cases, usually with only minimal improvement [4].

The incidence of alopecia areata during anti-TNF- α therapy is unknown as there are no prospective controlled studies. Another open question is whether alopecia areata is actually induced by the medication, or whether this is simply a causal relationship which indicates that anti TNF- α therapy is not effective in preventing development of alopecia areata in predisposed individuals. Since TNF- α inhibitors are used for the treatment of autoimmune diseases, this patient population is drastically more susceptible to the development of other immune mediated conditions, including alopecia areata. These questions must be further explored.

Psoriatic Alopecia: The use of TNF- α inhibitors has become a staple of psoriasis treatment. This comes as no surprise, as TNF- α has been shown to be pivotal in the development of psoriasis [36]. Interestingly, TNF- α inhibitors also have a paradoxical effect of inducing psoriasis in between 1.5%-5% of patients [37,38]. This is thought to occur due to the complex interaction between TNF- α and interferon (IFN) α [39,40]. Plasmacytoid dendritic cells (pDCs) produce IFN- α , a pro-inflammatory cytokine that has been shown to cause psoriasis [41,42]. TNF- α acts on the pDCs and causes a decrease in the production and release of IFN- α [39]. It is hypothesized that through their indirect action in increasing IFN- α , TNF- α inhibitors have the ability to induce psoriasis. Interestingly, the majority of these patients do not have a personal or family history of psoriasis.

In our review of the literature, we found 19 cases of TNF- α inhibitor induced psoriasis leading to alopecia (Table 2). Interestingly, this was reported with infliximab and adalimumab but not etanercept. Symptoms ranged from patchy alopecia to total scalp hair loss. In addition to the scalp, these patients exhibited psoriatic lesions on the trunk, axillae, extremities, genitals, and palms/soles. The onset of hair loss ranged from two [43,44] to 46 [45] months after the TNF- α inhibitor was begun, with an average latency period of 8.6 months. There were 11 females and eight males. The patients were receiving anti TNF- α therapy for Crohn's disease, ulcerative colitis, ankylosing spondylitis, juvenile idiopathic arthritis, and Behçet's disease.

Patients with TNF- α inhibitor induced psoriatic alopecia had a generally positive prognosis, as greater than 75% achieved scalp lesion clearance and complete hair regrowth after the medication was discontinued. Virtually all of the patients had some improvement in symptoms. One patient continued to exhibit diffuse patchy alopecia after adalimumab was discontinued, and hair loss was only halted after the initiation of cyclosporine 3mg/kg/day [46]. Topical steroids were applied in the majority of the cases although they appeared to have little positive effect without concomitant discontinuation of the TNF- α inhibitor. In three cases, the medication was continued and improvement was still appreciated with topical agents. Scarring alopecia, documented by pathology, occurred in 16% of the cases (three of 19 patients). Scarring alopecia is a possible evolution of

severe scalp psoriasis which has been linked to severe inflammation and sebaceous gland destruction [47].

There are multiple cases in the literature describing psoriasiform eruptions of the skin occurring in parallel with alopecia areata [28]. This presents the clinical challenge of differentiating TNF- α induced psoriatic alopecia and TNF- α induced alopecia areata. Doyle et al. proposed that this may in fact represent a distinct entity referred to as "psoriatic alopecia/alopecia areata-like reaction secondary to anti-TNF treatment." [35] The authors suggest that this can be diagnosed by histopathology where the presence of plasma cells and eosinophils can be used to distinguish "anti-TNF induced alopecia" from psoriatic alopecia and alopecia areata. It remains unclear whether this in fact represents a distinct clinical entity or rather a subset of the aforementioned diseases.

Lichen Planopilaris: Lichenoid drug reactions are a well-established adverse reaction to TNF- α inhibitors [48]. A rare but reported subcategory includes TNF- α inhibitor induced lichen planopilaris (LPP). LPP represents an immune-mediated inflammatory disorder which causes a scarring alopecia of the follicular apparatus [49]. There have been three reported cases to date of LPP occurring during treatment with a TNF- α inhibitor (Table 3). The diagnosis was confirmed in each case by histopathology. The patients were being treated for psoriasis and psoriatic arthritis.

Alopecia occurred between eight and 11 months after the initiation of therapy and varied widely. Two of the patients had focal scalp involvement with alopecia occurring as a patch in the frontal region [49] and along the temporal region and eyebrows [50], respectively. The third patient demonstrated symptoms diffusely throughout the temporal and occipital region of the scalp [51]. The ages ranged from eight to 56 years.

These patients had a relatively poor prognosis. In two cases, the TNF blocking agent was continued because of the patients' positive response to a previously refractory psoriasis. The lesions failed to improve after the addition of topical steroids and topical tacrolimus [49] and oral deflazacort [50], respectively. The third patient was initially taken off therapy with etanercept and the lesions disappeared with cyclosporine, NSAIDs, and topical steroids [51]. After a recurrence of severe psoriatic arthritis, he was restarted on etanercept and the LPP recurred with new areas of involvement. Etanercept was permanently stopped but the alopecia did not improve with methotrexate and NSAIDs.

Drug-Induced Lupus Erythematosus: Drug-induced lupus erythematosus (DILE) is an established complication of TNF- α inhibitors [52]. Classic symptoms include myalgia, arthralgia, rash and serositis in conjunction with abnormal laboratory values [52]. Rarely, alopecia can occur [52-55]. Carlson et al. described a 48-year-old woman who developed DILE after two years of treatment with etanercept for rheumatoid arthritis diagnosed after she presented with a two week history of diffuse hair loss, skin lesions, and abnormal laboratory values [55]. After discontinuing etanercept and receiving prednisone, her symptoms improved. After seven months, she had complete hair regrowth and her laboratory values normalized. In a French national study, de Bandt also described a patient who developed alopecia as a symptom of DILE [53]. The patient was being treated for erosive rheumatoid arthritis. The specific TNF- α inhibitor used was not disclosed.

Table 2: Psoriatic Alopecia during Treatment with TNF- α Inhibitors.

Age	Gender	TNF- α Inhibitor	Time Lapse until Onset of Alopecia Areata (months)	Site of Involvement	Management	Outcome	Manuscript
30	F	Adalimumab	2	Palms/Soles, Scalp	Adalimumab discontinued; no improvement on topicals and extensive hair loss ensued, hair loss halted after cyclosporine 3mg/kg/day	Hair loss halted	Papadavid [46]
28	M	Infliximab	6	Palms/Soles, Scalp	Infliximab discontinued	Lesion clearance	Papadavid [46]
22	M	Infliximab	5	Scalp	Infliximab discontinued	Lesion clearance	Papadavid [46]
19	F	Adalimumab	3	Scalp, Abdomen, Trunk, Extremities	Adalimumab discontinued	Lesion clearance and complete hair regrowth	El Shabrawi-Caelen [43]
31	F	Adalimumab	2	Scalp	Not given	Scarring alopecia	El Shabrawi-Caelen [43]
30	F	Infliximab	3	Palms/Soles, Scalp, Extremities, Trunk	Infliximab discontinued; topicals, cyclosporine	Improvement	Manni [40]
32	M	Infliximab	10	Scalp, Abdomen, Trunk, Extremities	Infliximab discontinued; topical clobetolol propionate	Lesion clearance and complete hair growth	Medkour [38]
49	M	Infliximab	6	Scalp	Infliximab discontinued	Initial lesion clearance, lesions recurred after infliximab restarted	Sfikakis [37]
43	M	Infliximab	7	Scalp, Extremities	Infliximab discontinued	Initial lesion clearance, lesions recurred after infliximab restarted	Sfikakis [37]
7	F	Adalimumab	9	Scalp, Ears, Heels	Topicals and cyclosporine; adalimumab switched to abatacept; methotrexate	Scarring alopecia	Perman [44]
11	M	Infliximab	26	Scalp, Trunk, Genitals	Infliximab continued; topicals and systemic antibiotics	Lesions clearance	Perman [44]
16	M	Infliximab	5	Scalp, Face, Trunk, Extremities	Infliximab switch to adalimumab; topicals	Lesion clearance	Perman [44]
14	F	Infliximab	2	Scalp, Face	Infliximab discontinued; topicals and methotrexate	Lesion improvement	Perman [44]
18	F	Infliximab	7	Scalp	Infliximab discontinued; topicals	Scarring alopecia	Perman [44]
26	F	Infliximab, Adalimumab	3	Scalp, Axillae, Umbilicus	Infliximab switched to adalimumab; topicals, methotrexate	Lesions cleared but patient continued to have flares	Osorio [45]
31	F	Infliximab	9	Scalp, Axillae, Genitals	Infliximab discontinued; topicals, methotrexate	Lesion clearance	Osorio [45]
23	F	Adalimumab	46	Scalp, Axillae	Adalimumab continued; topicals	Lesion improvement	Osorio [45]
30	M	Adalimumab	11	Scalp, Axillae, Genitals	Adalimumab discontinued; topicals, methotrexate, corticosteroids	Lesions clearance	Osorio [45]
25	F	Adalimumab	2	Scalp, Axillae, Chest, Genitals	Adalimumab discontinued; topicals, methotrexate, corticosteroids, cyclosporine	Mild Improvement	Osorio [45]

Androgenetic Alopecia/Telogen Effluvium: In rare cases, TNF- α antagonists have been found to precipitate androgenetic alopecia. Lee et al. described a 39-year-old woman who developed androgenetic alopecia after being treated with adalimumab for rheumatoid arthritis [26]. The patient also exhibited telogen effluvium [26].

Conclusion

TNF- α antagonists are an exciting new class of medication used for the treatment of many autoimmune diseases previously refractory to conventional therapies. As their use is becoming more prevalent, their side effects are becoming better documented. One little-known complication that has become more evident in recent years is alopecia.

TNF- α inhibitor induced alopecia is especially difficult for the physician to manage because there are no well-defined treatment guidelines and many treatment strategies come from anecdotal experience. Although there are many reports of its occurrence in the

literature and in postmarketing surveillance, there are few clinical trials where it is directly studied and its prevalence is therefore hard to estimate. It is also difficult to determine whether certain anti TNF agents are more likely to cause alopecia than others.

When the physician encounters new-onset alopecia in a patient on anti TNF- α therapy, the risk/benefit ratio must be weighed before any change in therapy is considered. TNF- α inhibitors have the ability to induce disease remissions in patients with debilitating autoimmune conditions refractive to traditional therapies. In some patients the benefit from treatment may outweigh the risk of permanent hair loss. For this reason, it is important for the physician to handle each situation case-by-case, taking the patient's priorities into consideration. As a general rule, we recommend switching to another medication in patients with alopecia areata or psoriatic alopecia occurring during anti TNF- α therapy. This can include another TNF- α inhibitor, or a different class of immunomodulating drug such

Table 3: Lichen Planopilaris during Treatment with TNF- α Inhibitors.

Age	Gender	TNF- α Inhibitor	Time Lapse until Onset of Alopecia Areata (months)	Site of Involvement	Outcome	Author
37	M	Infliximab 5mg/kg every 8 weeks	11	Hair loss in the frontal and temporal regions of the scalp and eyebrows	Infliximab continued; scalp and eyebrow lesions stabilized after deflazacort 35 mg/day; alopecia remained stable	Fernandez-Torres [50]
56	F	Etanercept 50mg weekly	8	Diffuse hair loss in the frontal and occipital regions of the scalp	Hair loss stabilized after Etanercept was discontinued; after recurrence of severe psoriatic arthritis, etanercept was reinstated and the alopecia and erythema recurred with new areas of involvement; etanercept was again discontinued and symptoms remained stable	Garcovich [51]
8	M	Etanercept 0.8mg/kg/week	Not Given	9x8cm patch on the frontal region of the scalp	Etanercept was continued and the alopecia failed to improve after topical steroids and topical tacrolimus	Abbasi [49]

as methotrexate or cyclosporine, depending on the condition being treated. We also recommend the application of topical steroids under occlusion.

TNF- α blockers are a very useful class of medication that have the ability to drastically improved the lives of patients. As such, the side effect of alopecia may be considered by some to be relatively inconsequential compared to the debilitating disease being treated. The purpose of this paper is not to discourage the use of anti TNF- α therapy but to inform physicians about this potential side effect so that they may be more able to manage it if encountered in their practice.

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