

Sobia Noreen^{*} Fahad Pervaiz[†] Irsah Maqbool[‡] Madiha Saleem[§]**Alopecia: Review of Epidemiology, Pathogenesis, and Novel Treatment Strategies****Abstract**

Alopecia is an autoimmune and non-communicable disorder. The immune system, especially T-lymphocytes, present around the hair follicle attacks, cause inflammation and loss of hair from some or all areas of the scalp. It is highly prevalent in the United States; an estimated 4.5 million are affected by this disease. Finasteride and minoxidil are mostly used to treat alopecia in the form of solutions and gels. However, their use has been limited due to severe adverse effects observed during therapy. This article summarizes the epidemiology, risk factors, pathophysiology, sign and symptoms, and diagnostic parameters with a focus on novel treatment strategies.

Key Words: Alopecia, Hair Loss, Etiology, Pathogenesis, Diagnostic Parameters

Introduction

Alopecia is considered a common form of scalp hair loss, often referred to as male pattern baldness disease. Its prevalence in women is lower than in men. It is determined by the presence of an androgenic complex and the rate of genetic predisposition. It is not a severe disease in terms of medical perspective, but it is an unwanted and stressful condition. Another common type of alopecia is alopecia areata, an autoimmune disease. Loss of hairs is occurred due to genetic predisposition and environmental factors (infection and psychological stress). Its progress in severe conditions results in complete hair loss termed as alopecia totalis or alopecia Universalis (total loss of body hair) ([Darwin](#)

[et al., 2018](#); Ellis, Sinclair, & Harrap, 2002; Fricke & Miteva, 2015).

Epidemiology

Alopecia Arata (AA) is the most common inflammatory disease. It affects both the children (> 3years) and adults. In the United States, it is estimated that 4.5 million people were affected by alopecia areata. Some studies reveal that men aged 21 to 30 were affected by this disease (Lee et al., 2020). Alopecia Arata increased the risk of other autoimmune disorders (16%) (Gilhar, Etzioni, & Paus, 2012), as shown in table 1.

Table 1. Risk Factors Associated with Alopecia

Disorders	Percentage ratio in patients
Lupus Erythematosus	0.6%
Vitiligo	4%
Autoimmune thyroid disease	8-28%

Pathophysiology**Normal Hair Cycle and Disordered Cycling in Alopecia**

It is essential to know the average hair growth period and immunology of hair follicles for the sake of clinical presentation and diagnosis of alopecia. Mature hair

follicles divide into the upper segment (Infundibulum and isthmus) and lower segment (stem and bulb). The normal hair cycle consists of phases of growth, anagen phase, catagen phase, and telogen phase Figure 1.

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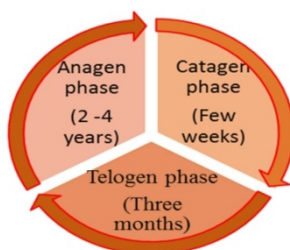


Figure 1: Duration of Phases of Hair Growth in Normal Hair Cycle

The hair follicle consists of the papilla, matrix, root sheath, hair fibre, and bulge. The infolding of the epidermis forms hair follicles into the dermal layer. The follicular papilla lies in the centre of the follicular bulb. Volumes of dermal papilla control the size of the hair follicle. The hair shaft consists of three layers medulla, cortex, and hair cuticle. The medulla contains few layers of round cells containing glycogen. The cortex forms the bulk of hair follicles. Matrix cells, which are termed undifferentiated epithelial cells, present in the bulbar region of hair follicles, which play a central role in hair growth and the inner root sheath (Cotsarelis, Sun, & Lavker, 1990; Mirzoyev, Schrum, Davis, & Torgerson, 2014).

Anagen Phase

The anagen phase (growing phase) is the first stage of hair growth. Hair follicle at its deepest level, 85% of hairs in this phase. Hair matrix surrounds the dermal papilla. Duration of this phase responsible for the final length of hair. It usually lasts for 2-3 years. Epithelial cells often intersprinkles with the pigment-

producing cells, Melanocytes (impart color to newly forming hairs). Mitosis involves producing cells that form significant hair structures, fibre, and inner root sheath (Perera, Yip, & Sinclair, 2014).

Catagen Phase

The second and shortest transition stage occurs at the end of the anagen phase. At the end of the anagen phase mitosis process declines and ceases. The lower part of the follicles undergoes apoptosis. The basement membrane surrounding the follicles becomes thickened to form a glassy membrane. It lasts for a few weeks; 1% to 3% of total hairs are always in this phase (Bhat, Sajad, & Hassan, 2014).

Telogen Phase

The resting stage of hair follicles usually lasts for about three months. It is also called the quiescent period between the completion of follicular regression and the next anagen phase (Mubki, Rudnicka, Olszewska, & Shapiro, 2014a, 2014b) Fig 2.

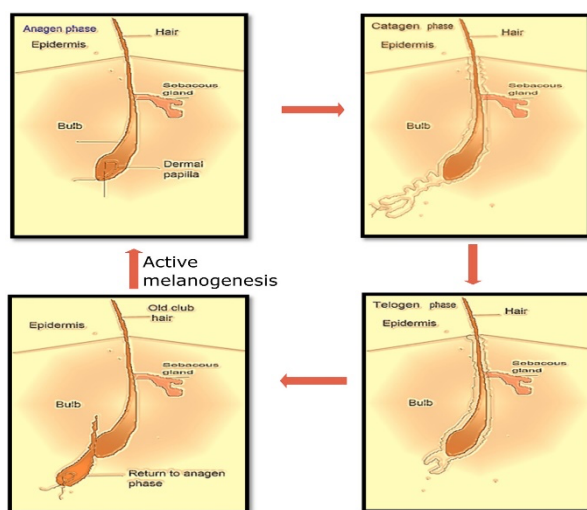


Figure 2: Hair Cycle in Alopecia

Role of Androgen Receptor During the Normal Hair Cycle

Androgen receptor is necessary for male development for normal functioning of organs in the whole adult life span. It also plays a role in hereditary characteristics as well as in some diseases. Testosterone gets entry into the cell and converted into dihydrotestosterone by the enzyme 5 α -reductase. This DHT forms complex with the

androgen receptor and moves into the nucleus, where the transcription control of androgen-dependent genes are already present in the nucleus to control the loss of hair (Thornton et al., 2003) Fig 3.

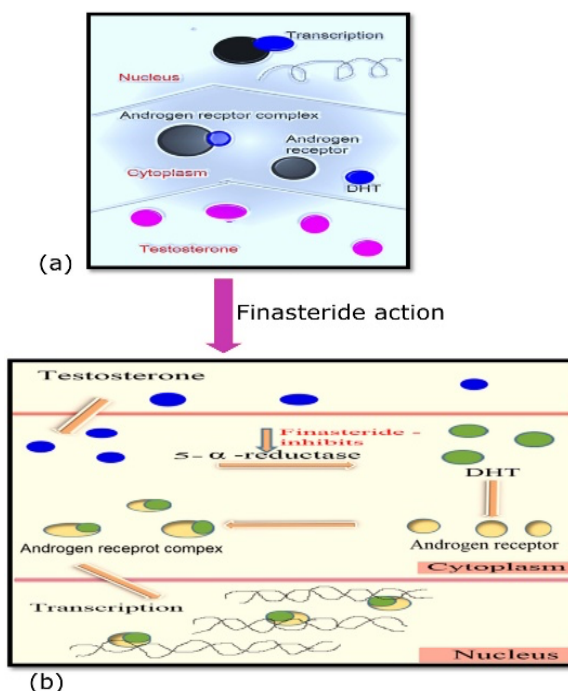


Figure 3: Involvement of the Androgen Receptor in Normal Hair Cycle (a) Mechanism of Action of Finasteride (b)

Factors Affecting Hair Growth

Many factors affect the hair cycle's growth like chemotherapeutic drugs, hormonal imbalance during stress, and post-pregnancy. Hair follicles respond to androgens and increase the duration of the anagen phase. Scalp hair follicles show regressive behavior towards the androgen level. In alopecia, enzyme 5 α reductase converts the androgens into a more potent form. An increase in the concentration of 5 α -reductase forms more and more involved with DHT; due to this androgens, responsive genes involved in male baldness are identified and produced baldness in males ([Kretzschmar, Cottle, Schweiger, & Watt, 2015](#); Sinclair, 2002). Growth hormones also increase the regression phase. An increase and decrease in thyroid hormone level also induce alopecia (Johnstone & Albert, 2002).

Signs, Symptoms, and Diagnosis

Alopecia areata develops due to abnormal hair cycling and early entry of anagen phase into the telogen phase. In the form of small patches, sudden hair loss occurred when immune systems mistakenly attack the hair follicles within a few days or weeks. If it is diagnosed at early stages involving just a few hair loss patches, it can be easily treated; otherwise, it becomes more severe and develops alopecia totalis or alopecia Universalis. Alopecia produces small changes in fingernails and toenails, such as white lines, rough appearance. An increase in the concentration of eosinophils is the diagnostic feature for AA (Alkhalifah, Alsantali, Wang, McElwee, & Shapiro, 2010). T-lymphocytes, dendritic cells CD4⁺,

CD8⁺, mast cells, and natural killer cells are the inflammatory cells that produced abnormalities in the hair life cycle and start apoptosis (Gilhar et al., 2012;

Motofei et al., 2016; Samrao, Chew, & Price, 2010)
Table 2.

Table 2. Diagnostic Parameters for Alopecia

Tests	Findings
Family history	Hypothyroidism, hyperthyroidism and autoimmune disorders
Physical examination	Ocular abnormalities and yellow dots or exclamation mark of hair and nailchanges characterized by pitting
Lab tests	Thyroid function test
Histologic examination	Biopsy specimen obtained to find out.

Treatment Plan

Patients with alopecia behave; differently, some patients, especially children, find it challenging to survive with AA. If alopecia persists for a prolonged

period, patient behavior must be positive, self-accepting, and show compliance towards active treatment Fig 4.

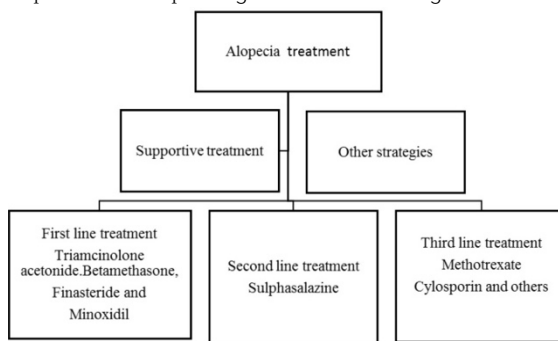


Figure 4: Treatment Options for Alopecia

Supportive Treatment

Alopecia can be treated symptomatically with the help of a psychologist to get relief from stress condition. However, chronic conditions require active treatment. It has some disadvantages like; it is time-consuming and produces undesirable side effects (Ohyama, Shimizu, Tanaka, & Amaqai, 2010).

First-Line Therapy

First-line therapy includes Intralesional corticosteroids, topical corticosteroids, 5- α reductase inhibitors, and minoxidil to treat alopecia (Wasserman, Guzman-Sanchez, Scott, & McMichael, 2007).

Intralesional Corticosteroids

Triamcinolone acetonide injection is a widely used agent to treat alopecia. A dose of 5mg/ml is the preferable therapeutic concentration for the scalp and is repeatedly administered into the deep dermis or just below the dermis at 4-3 weeks intervals. It produces some side effects, such as skin atrophy and

telangiectasia. The patient must be treated with topical anaesthesia before treatment to alleviate injection pain (Kumaresan, 2010).

Topical Corticosteroid

Topical corticosteroids are prescribed to treat

alopecia in the form of ointments, lotions, creams, foams, gels. The most commonly used corticosteroids are 0.1% betamethasone valerate foam, 0.05% clobetasol propionate ointment. 0.05% Betamethasone dipropionate lotion is also used for the regrowth of hair. Folliculitis is the significant side effect of topically applied corticosteroids (Madani & Shapiro, 2000; Răcz, Gho, Moorman, Noordhoek Heqt, & Neumann, 2013).

5- α Reductase Inhibitors

Finasteride is an FDA approved type II 5- α reductase inhibitor for treating alopecia in men and benign prostatic hyperplasia (BPH) **Fig 3**. Dutasteride,

alfatradiol are also used for alopecia management (Prager, Bickett, French, & Marcovici, 2002).

Antiandrogens

Ketoconazole also an antiandrogen agent and improve hair growth. It is an antifungal agent. It is used mostly to treat dermatitis and dandruff. Spironolactone is also inhibiting the androgen receptors and their production. It is mostly used to manage alopecia in females due to its feminizing side effects in men, significantly increasing the risk of infertility in men. Flutamide shows anti-androgenic activity with marked side effects in women ([Yip & Sinclair, 2006](#)).

Minoxidil

Minoxidil is available in various topical dosage forms with other agents such as adjuvant therapy. The dose of 1% and 5% minoxidil solution or foam used to get the beneficial effects of therapy. Contact dermatitis and facial trichinosis are the adverse effects observed during the treatment (El Taieb, Ibrahim, Nada, & Seif Al-Din, 2017; Pervaiz et al., 2020).

Anthralin

The dose of 0.5% -0.1% Anthralin cream was used to treat severe alopecia in controlled trials and open study trials. Therapeutic response was observed in 25% of patients. Adjuvant therapy with minoxidil showed a cosmetic response in 11% of patients. Anthralin required a high dose or daily dosing to get beneficial effects to treat alopecia with some adverse effects staining of the skin and mild or severe irritation (Tang, Cao, Pelech, Lui, & Shapiro, 2003; Wu, Wang, Ratnaparkhi, & Bergfeld, 2018).

Topical Immunotherapy

Diphenylcyclopropenone is an immunotherapeutic agent to treat alopecia. It is a light, sensitive agent. At the start of treatment, 2% solution was applied to the scalp. Diphenylcyclopropenone, 0.001% applied on the half scalp after two weeks. Mild dermatitis was observed due to the gradual increase in concentration. It should be used weekly by a professional person and protected from sunlight. If a response is not seen after six months duration of therapy, it must be discontinued. Squaric acid dibutyl ester is a costly agent and applied once or twice a week. It showed instability towards the organic solvent acetone (Singh & Lavanya, 2010; Van der Steen & Happle, 1993).

Second-Line Therapies

Sulphasalazine is mostly used to treat autoimmune diseases, especially rheumatoid arthritis but sometimes also prescribed for alopecia treatment. It combines two compounds, sulphapyridine, and 5-aminosalicylic acid, attached to the diazo bond. It showed immunosuppressive action by suppressing the proliferation and synthesis of T-lymphocytes. antibody production and tumor necrosis factor-alpha. Sulphasalazine dose was prescribed from 500mg -1g twice a day or later thrice a day. Some specific tests like complete blood count, creatinine level, liver function test, and glucose-6-phosphate dehydrogenase should be conducted with Sulphasalazine's continuous therapy. Sulphasalazine therapy induces side effects that include dizziness, headache, GIT distress (Aghaei, 2008).

Third-Line Therapies

Systemic corticosteroids, methotrexate, cyclosporin, azathioprine are also used to treat alopecia.

Systemic Corticosteroids

An oral dose of prednisone 300 mg and prednisolone 500 mg were prescribed for hair regrowth once a month or once a week, respectively. Systemic corticosteroids produce side effects that make their use limited in treating alopecia (hyperglycemia, dysmenorrhea, hypertension, and immunosuppression) ([Kar, Handa, Dogra, & Kumar, 2005](#)).

Methotrexate

Methotrexate is prescribed for treating alopecia along with a dose of 15-25 mg in a week or combination with systemic corticosteroids with low doses such as prednisone 10-20 mg per day. Nausea and leucopenia are adverse effects observed during therapy (Batalla, Flórez, Abalde, & Vázquez-Veiga, 2016; Hammerschmidt & Mulinari Brenner, 2014).

Cyclosporin

Cyclosporin is not commonly prescribed to treat alopecia due to its adverse effects, especially nephrotoxicity, immune suppression, and hypertrichosis. It is favorably prescribed in patients with elevated serum levels of IL18 and lower levels of soluble receptor IL2 (Kim et al., 2008).

Azathioprine

Azathioprine inhibits the proliferation of T and B cells and inhibits DNA synthesis. Azathioprine is a

thiopurine analog and used to treat autoimmune diseases ([Farshi, Mansouri, Safar, & Khiabanloo, 2010](#)).

Other therapies employed for the treatment of alopecia summarized in table 3. Some of which are described below.

Other Strategies

Table 3. Other Therapies for Alopecia Treatment

API	Topical/Oral/Systemic
Garlic extract	Topical gel
Betamethasone valerate	Topical cream
Azelic acid	Topical
Zinc supplementation	oral
Tri-iodothyronine	ointment

Biologics Drugs

These drugs are proved ineffective for the treatment of alopecia (Price, 2003).

Hair Transplantation

It is a surgical procedure. It is mostly used to treat alopecia in males (Jiménez & Poblet, 2013).

Laser Therapy

THE 308-nm laser therapy is considered an effective therapy for patchy alopecia (Zakaria, Passeron, Ostovari, Lacour, & Ortonne, 2004).

Conclusion

Alopecia is a complex disease with a compliant projection. Though a large number of patients will reconcile spontaneously, other patients may experience chronic disease. There are no FDA-approved managements and cure; however, corticosteroids are reflected as the first-line therapy. Still, there is a need to extensively review the future avenues and require more research to elucidate advanced cure.

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