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<th>Description</th>
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<tr>
<td>AA</td>
<td>Alopecia Areata</td>
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<tr>
<td>Ach</td>
<td>Acetylcholine</td>
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<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
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<td>ADTA</td>
<td>acute diffuse and total alopecia</td>
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<td>AGA</td>
<td>Androgenic alopecia</td>
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<tr>
<td>AI</td>
<td>Alopecia Incognita</td>
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<tr>
<td>AT</td>
<td>Alopecia Totalis</td>
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<tr>
<td>AN</td>
<td>Alopecia Neoplastica</td>
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<tr>
<td>AU</td>
<td>Alopecia Universalis</td>
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<tr>
<td>CGRP</td>
<td>calcitonin gene related peptide</td>
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<tr>
<td>cT</td>
<td>cardiac troponin</td>
</tr>
<tr>
<td>CTE</td>
<td>Cicatricial telogen effluvium</td>
</tr>
<tr>
<td>DPCP</td>
<td>Diphenylcyclopropenone</td>
</tr>
<tr>
<td>DEBR</td>
<td>Dundee experimental bald rat</td>
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<tr>
<td>DLE</td>
<td>Discoid Lupus Erythematosus</td>
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<td>DLQI</td>
<td>Dermatology life quality index</td>
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<tr>
<td>eSOD</td>
<td>Erythrocytes superoxide dismutase</td>
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<tr>
<td>FOXP3</td>
<td>Fork Head Box Protein 3</td>
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<tr>
<td>GWAS</td>
<td>Genome wide association studies</td>
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<tr>
<td>HFs</td>
<td>Hair Follicles</td>
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<td>HLA</td>
<td>Human leukocyte antigens</td>
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<td>HLS</td>
<td>hair loss severity</td>
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<tr>
<td>ICOS</td>
<td>Inducible Costimulator</td>
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ICOSLG  ICOS ligand
IgE  Immunoglobulin E
IL  Interleukin
Kv  Voltage-gated potassium channels
LPP  Lichen planopilaris
MCP-1  Monocyte Chemoattractant Protein-1
MDSCs  Myeloid-derived suppressor cells
MICA  Major Histocompatibility Complex class chain-related gene A
MHC  Major histo-compatibility complex
NAMCS  National ambulatory medical care survey
NK  Natural Killer
NLCs  Non Structured Lipid Carrier
PAP-1  5-(4-Phenoxybutoxy)-Psoralen
QoL  Quality Of Life
SADBE  Squaric Acid Dibutylester
SCID  Severe combined immunodeficiency mice
SLE  Systemic Lupus Erythematosus
TNF  Tumor Necrosis Factor
VDR  Vitamin D receptors
1A-ABSTRACT

Alopecia areata (AA) is an auto-immune disease of a recurrent non scarring type of hair loss that can affect any hair-bearing skin of the body and can be manifested in many different patterns. The exact pathogenesis of AA till now is not completely known, it can be an autoimmune, genetic or environmental factor (Ganjoo et al. 2013). Although AA is an autoimmune disease and controlled by activated T cells and considered as a polygenic disease, it is a benign condition and most patients are asymptomatic. It can be caused also by an emotional and psychosocial distress (Norris 2003). AA is a type of hair loss that typically causes patches of baldness. The most cases of AA are single round patches to a large surface area called Alopecia totalis (AT) or to be of all the body and scalp called Alopecia universalis (AU) (Bansal et al. 2013). Hair loss can be life threatening and cause death in mammals, like polar bears, seals and reindeer because of a big loss of hair volume, but not in human beings (Ito 2010).

There is no need for treatment of AA in some cases, where the hair may regrow, typically after several months. In other cases, treatments can be effective and complete recovery observed, although some of the cases of baldness can be permanent, or difficult to be treated after long time of treatment, even with the use of more than one drugs for the same patient or with high doses of drugs which may be effective for others who can respond to the treatment in short period of time and having an accepted result. In this study I try to explain most of the drugs that are used to treat AA including two new combination formulas, which can be useful for the treatment of all types of AA involving also androgenic alopecia.

These combination formulas can be helpful when the patient does not adequately respond to a mono-therapy with e.g. minoxidil, corticosteroids or other drugs. AA is a common disease which can be seen in many people all over the world with no limit between women or men. It is also one of the diseases that are related to the psychological situation of the patient which may become worse when the patient cannot overcome this disease. Therefore, treatment is urgent for those patients in order to return them to their normal life so soon as possible.
**1B-ZUSAMMENFASSUNG**


AA ist eine häufig auftretende Erkrankung, die weltweit bei Männern und Frauen gleichermaßen vorkommen kann. Es ist auch eine Erkrankung mit psychosomatischer Komponente und das Krankheitsgeschehen kann bei erfolgloser Therapie weiter verschlimmert werden und deshalb sollte unmittelbar mit einer geeigneten Therapie begonnen werden.
2-INTRODUCTION

AA is a non-scarring auto-immune disease of the hair follicle mediated with T lymphocytes; it can be described by the loss of hair in ovary or round shape in one or multiple areas, at any place of the body like scalp, eyelashes, eyebrow, brat, etc. AA is related to the T-cells which have a big role in the loss of hair follicles at any part of the human body involving nails, congenital area, etc. and can be present at any age of life (Wang et al. 2012). The regrowth of hair is common to occur, or it can be worse due to many causes. One of the causes is the association with other diseases like atopic dermatitis or diabetes mellitus (Wasserman et al. 2007).

Although AA can occur equally in both male and female, there is evidence that black females may be more often affected by AA. Histopathological examination is essential for the diagnosis although some characteristic dermatological features can be helpful in addition to other diagnosis methods which are not less important than the histopathological examination (Wang et al. 2011). As I will mention in this thesis, AA can be also a genetic disease where it occurs in identical twins as reported in a study from Rodriguez et al. (2010). AA can be classified in many types which are also listed in this thesis, such as alopecia totalis, alopecia universalis, etc. (Amin et al. 2013). AA is a smooth bald patch of the scalp, but when the bald surface is not present, then this type is called alopecia areata ingonita (Park et al. 2013). Patches of alopecia with demarcated borders between normal and affected scalp is the most distinguished feature of AA (Price et al. 2005).

The course of AA is capricious and unpredictable, where the patches seem to be spontaneously regrown within a year and can be spread or progress to other areas on the body with time. The regrowth of hair is common to be observed in most of the patients, or it can become worse due to many causes that will be also mentioned in this thesis. The National Alopecia Areata Registry Database in USA shows that there are also other causes like the association with other autoimmune diseases such as Hashimoto thyroiditis, vitiligo, and diabetes mellitus. Price et al. (2008) also reported that 20% of AA cases show no signs of regrowth even after 10-15 years,
while 12% of the patients with AA may develop an autoimmune disease (Barahmani et al. 2009).

The environmental factors and genetic predisposition may play an important and a big role in triggering the initiation of this disease. There is also an increase in the morbidity in those patients who suffer from AA with complicated history of the disease (Madani et al. 2010). New studies show that AA is a complex disease which is mainly due to the action of multiple genes with or without the environmental or psychological factors as well (Petukhova et al. 2011). AA can be seen mostly in young patients or even in children under 16 years (Price 2013).

Till now the pathogenesis of the disease remains incompletely explained and it needs more researches in order to overcome it (Seetharam et al. 2013). This thought is listed in most studies that are mentioned in literature. Although the most cases of AA can be related to other diseases or causes (Alkhalifa et al. 2011), it had been explained that AA can be without any symptoms or signs and there is no other related disease such as vitiligo or thyroid disease (Price 2013). There are also reports of suicide in those patients with long standing AA which is more common in 3-5 decades (Dehghan 2013), while another study considered that it can be more common in the 2nd and the 5th decade (Alkhalifa et al 2010). The course of AA is unpredictable and there is a different rate in response to the treatment. In 1%-2% of cases it can develop to severe cases and involves the complete scalp, which is called Alopecia totalis (Amin et al. 2013).

Recovery rate varied from one patient to another depending on many factors, but it can be in a range of 34–50% within a year (Açikgöz et al. 2013). AA accounts for 2-3% of the new dermatology cases in UK and USA, 3.8% in China, and 0.7% in India. In the general population it was estimated at 0.1%-0.2%, with a life time risk of 1.7%; other studies reported that it occurs more often in males than in females (Seetharam 2013, Farhsi et al. 2008 ), where approximately 60% of patients develop AA before the age of 20 years (Sardesai et al. 2012).

AA may in general affect approximately 5.3 million people in the USA (Petukhova et al. 2010). The course of the disease is unpredictable and the responses to all types of the treatments, as a single drug or in a combination, are variable (Ganjoo et al. 2013). Kar et al. (2013) considered AA a worldwide disease, as a lymphocyte cell-mediated inflammatory type of hair loss without
atrophy. One of the major contributing factors for AA is the major histocompatibility complex (MHC) (Duvic et al. 2001).

As a common disease, AA can be encountered from dermatologists with a frequency of 0.7% and 3.8% of the patients attending dermatological clinics. Another study shows that 85.5% of Asian patients have AA before 40 years of age (Alkhalifa et al. 2010, Price 2008). It is reported that 60% of patients develop AA before the age of 20 years and family history is present in 20% of cases, while patients with an incidence of 3.8% - 85.5% had their episode before the age of 40 in China (Wasserman et al. 2007). The most common site of presentation is scalp; there are other sites which are also affected such as the beard, eyebrows, eyelashes, body, armpits, pubic region; nails involvement in the form of pitting, punctate depressions, mottled lunular, onychomadesis, punctate, leukonhchia, trachyonychia, and pseudomycotic pachyonychia may also present (Rosenstein et al. 2010).

All patients with AA should be treated early, and require psychological support in addition to the prescription of drugs. A study placed in China used the dermatology life quality index (DLQI) which is a questionnaire of 10 questions, and each question refers to the previous 7 days. It covers symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment as dimensions of life. Each item scored 0-3. Scores are added to yield a total DLQI of 0-30; higher scores mean greater impairment of the patient’s quality of life (QoL). The mean DLQI was 5.8 ±5.6, which is a moderate limitation of QoL, varying according to sex, age of onset, hair pulling test, and family history of AA; the younger patients exhibited higher DLQI scores (Qi et al. 2014).

AA can be seen in patients who had other dermatological diseases like vitiligo, atopic dermatitis, psoriasis or systemic Lupus erythematosus (SLE), etc. It is also reported that there is a high prevalence of mood, depression and anxiety disorders in patients with AA (Amen et al. 2013). AA can be associated with other diseases and can appear at the same patches like vitiligo. Therefore, there are a lot of studies which suggest that AA and vitiligo are like apple and orange, so that they can be easily differentiated from each other (Harris 2013).
The pathogenesis of AA involves local angiotelectasis and vasculitis close to the hair follicle. Therefore, AA is commonly seen with SLE. Exclamation-mark hairs, black dots, broken hair and yellow dots are common in AA, while hair shaft thinning and hypopigmentation, angiotelectasis, perifollicular red dots, white dots and honeycomb pigment patterns are more common in SLE. The most common angiotelectasis presentation of SLE alopecia patches is interfollicular and polymorphous; but interfollicular arborizing vessels are significantly more common in no hair loss affected SLE regions. In AA hair-loss regions increase in hair was the earliest feature that appeared after treatment of both SLE and AA. The earliest feature that disappeared was hair shaft hypopigmentation in SLE and broken hair in AA (Ye Y et al. 2013).

AA can be treated with various drugs topically or systemically given. Local treatments do not alter the underlying conditions, while the systemic treatments can modify the course of the disease. Treatment may be dependent on different factors, such as extent of the disease and age of the patient (Rosenstein et al. 2010).

The most used and as effective considered therapies for AA are: intrallesional corticosteroid injections, minoxidil solution, topical use of anthralin ointment, topical use of sensitizers like diphencyprone, dinitrochlorobenzene or squaric acid dibutyl ester, oral mini pulse of oral steroids, or use of phenol 88% with dexamethasone pulse therapy (Kar et al. 2013).

In this thesis I will present the most drugs used for AA treatment. The predisposing genetic factors which are characterized by the presence of human leukocyte antigens (HLAs) like DQ3, DQ7, DR4, and DR11 are associated with autoimmune disease, and external triggers like psychological problems, stress, etc. The hair follicle autoantigen remains not fully identified, but melanocyte related protein has been suggested as a strong candidate. Melanocyte associated T cells epitopes are capable of functioning as autoantigens to induce AA in the human scalp and severe combined immunodeficiency mouse model (SCID). Both CD4+ and CD8+ T cells were required to induce AA like hair loss (Ito et al. 2013).
**3- ALOPECIA AREATA**

### 3.1 History of alopecia areata:

AA was first clinically described by Cornelius Celsus in 30 A.D; therefore AA is sometimes known as "Area Celsi", but the term AA was coined by Sauvages in 1760, in Lyons, France (Seetharam et al. 2013).

Other studies said that Hippocrates was the first who used the Term "Alopecia" which is literally translated as "Fox disease". He had described two types of this disease. The first is a complete loss of hair at any age, this type named today AT. The second one was Ophiasis which is literally translated as "Snake". Many searchers considered that AA can occur due to emotional or physical stress and trauma. Those causes are also believed to affect hair follicles via the nervous system or might be due to bacterial causes (Aldersmith 1897). Thin (1897) considered that AA could be associated with ringworm, but the disease does not spread through children at school. In an old study Robinson (1885) said that patchy hair loss could be induced by cutting nerves in the necks of cats. AA can be also related to the eye strain as another suggested cause of AA (Gardiner et al. 1945).

Patients of AA can show patches between fingers, and the finger nails are affected. Also monilia can be seen in scrapings from the nail plate and the nail bed, but these are not obtained from the patches of AA areata on the scalp (Dore et al. 1931). It could be related to the parasite. Others suggested that harming ringworm or syphilis could be the cause, because of sudden and rapid loss of hair as a patchy just like AA, where AA can be increased because of stress or due to anxiety when it is associated with other dermatological diseases (Hubble et al. 1944).

Another theory in the 20th century said that AA can be related to a trauma due to an accident where the cut of the scalp can lead with time to the development of AA, and this type called traumatic AA (Barber 1932).
Another study is one of the first studies which considered that AA as an autoimmune disease due to foreign invading organism attacks (Van Scott 1958). AA can be related also to dental cause as mentioned in a study from Lesclous (1997).

New et al. (1958) considered AA as a usual disease in etiology, prognosis and treatment. 20% of cases are of genetic origin, 50% of AA cases may develop AT or AU. They said that syphilis is the only systemic infection producing patchy alopecia. They said also that 75% out of 44 patients with AA are psychoneurotic, and 20% are psychotic or border of psychosis. Other causes for AA could be toxic, endocrine, neurogenic, local infections and focal or general infection. The main toxic effect is the appearance of lymphocytic infiltrate around the hair follicles and blood vessels or other appendages.

Thin (1882) suggested that the cause of AA is either an organism or a bacterium, and he suggested the use of sulfur for 2 months, because sulfur is destructive to minute organisms and prevents their rapid extension. He had also discovered that shaving of hair is without any benefit or does not arrest the disease. It even can spread to eyelashes and eyebrows, and the features of AA referred to the nerve hypothesis of the disease. AA can also be related to other diseases, mainly Down syndrome (Du Viver et al. 1975).

Dillaha et al. (1952) suggested that hormonal factors can modify the course of AA, and the treatment with systemic cortisone acetate is useful and recurrence can happen. Ammonia was the mainly used drug as a treatment of AA in past because of its effectivity against AA by irritating the patches of disease more than the use of spirit of turpentine or capsicum. Because improving the health of hair follicles achieved by using tonic medicines and good nourishing diet, they believed that AA is not of fungus or parasitic origin. Stowers (1875) explained that AA is more common in women than men, and there is no extreme remedy of AA. He also believed that this disease occurs with parasitic and none parasitic origin like other local stimulants, and that it can be treated by the use of tonic medicines like cod liver oil and mineral acids. Systemic steroids can be considered as one of the most used drugs in the past and nowadays (Unger 1973). During the past history till now there were many drugs used for the treatment of AA,
and most of the treatments are corticosteroids, which are used alone or in combination with other drugs.

A study from Reid et al. (2012) finds that the diagnosis of AA depends on the assessment of the hair loss severity (HLS) using dermatologist questionnaire. They said that HLS depends strongly on the quality of life of the patients more than the dermatologists rating. This study assessed using Skindex-16, a self-reported dermatology-specific QoL (quality of life) measurement tool, investigating QoL in patients with AA. The more severe is the patient’s hair loss rating.

Alopecia has many known psychosocial complications, including depression, low self-esteem, altered self-image, less frequent and enjoyable social engagement. Lack of physician counseling and education may contribute to more negative perceptions of hair loss.

3.2-Types of Alopecia Areata:

There are mainly three general types of AA:

- Alopecia Areata,
- Alopecia Areata Universalis (AU) and
- Alopecia Areata Totalis (AT).

AA is the most common of the disease in which hair loss occurs in round or oval patches. AU is the form of the disease in which all hair on the body and scalp is lost. This is the rarest form of AA. Hair loss on the scalp is classified as AT.

In general the following are the main types of AA:

- Alopecia Areata Focalis: hair loss in patches on the scalp or on any other parts of the body like face, abdomen, legs, Hands, knee, shoulders, etc.
- Alopecia Areata Totalis: hair loss on the scalp involving the eyebrows and eyelashes
- Alopecia Areata Universalis: loss of all body hair
- Alopecia Maligna: long history of AA which does not respond to treatment
• Ophiasis or Alopecia Areata Marginata: snake-shaped hair loss around the circumference of the head in the temporal, occipital and frontal areas
• Ophiasis Inversus: the inverse pattern of hair loss, which expands from the central to the marginal area of the head
• Alopecia Areata Diffusa or Alopecia Areata Reticularis: diffuse or reticular hair loss where separate bald patches are not present (Brzezińska et al. 2014).

Bansal et al. (2013) explained that most cases of AA are single round patches to a large surface area called AT. The following figures explain the most common forms of AA, localized as single or multiple patches (Figure 1), reticular hair loss as ophiasis as snake like shape along the posterior occipital and temporal margins (Figure 2). Sisaipho or called ophiasis inversus which is seen with alopecia including the temporal, frontal and partial scalp, mimicking androgenetic alopecia (Figure 3) or as linear distribution (Figure 4), small distinct patches may merge and form larger patches (Figure 5) (Seetharam 2013).

![Figure (1): Localized patch of alopecia areata.](image)

![Figure (2): Ophiasis](image)
The classification of AA is made depending on the condition of the patient, extent of the disease, and place of the hair loss area. Those types as mentioned above are also classified as follows:
AA is represented by the presence of alopecic patches or a different size plaque on the scalp. Ophiasis AA (snake like) is represented by a lattern of hair loss affecting the front parietal, temporal and occipital regions. Sisaipho AA also called as ophiasis inversus, is the hair loss affecting the entire scalp except the peripheral ring mimicking androgenic alopecia. Reticular AA is a numerous patches of hair loss on the scalp with areas of hair remaining in between. Alopecia diffusa is acute and generalized hair loss which is difficult to be diagnosed. Perinevoid AA is hair loss around a melanocytic nevus, and sometimes may occur in linear distribution (Barahmani et al. 2009).

AA may be classified according to the duration of the disease. If the duration is less than 1 year then it is AA transient, but if the duration of the disease is more than that, then it will be a persistent alopecia areata (AAP). AT as a subtype includes patients with a history of total scalp hair loss for more than 1 year. Tick bite alopecia is a localized telogen effluvium caused by an anticoagulant in tick saliva. Therefore, the follicles are undamaged (Whiting 2001).

Another type of alopecia is Alopecia Neoplastica (AN), defined as alopecia caused by the cutaneous infiltration of malignant cells from distant malignancy. Its pathology may be due to destruction by the direct infiltration of the hair sheath by the neoplastic cells, to fibroplasias caused by or in response to the neoplastic cells, and to injury by cytokines like interleukin-4, transforming growth factor - beta, and fibroblast growth factor.

AA can be classified according to the number of patches:

- **Mild:** It is characterized by three or less patches of alopecia; its diameter is less than 3 cm, or it can be considered as a disease limited to eyelashes and eyebrows.
- **Moderate:** This type is characterized by the existence of more than three patches of alopecia or by the presence of a patch with a diameter greater than 3 cm at the widest, and it is not alopecia totalis or universalis.
- **Severe:** it is either alopecia totalis or alopecia universalis (Amin et al. 2013).
3.3- Autoimmunity and Histopathology

The hair follicle is a unique mini organ.

The hair cycle has the following stages:

- anagen, the growth stage,
- catagen, the regression stage, and
- telogen, the resting stage

Each stage has its own unique immune milieu (Ito 2010). In the anagen phase the immune-privilege is the main intriguing feature, and its duration determines the type of hair produced and its length, where 100 hairs fall each day by reaching the resting phase (Headington 1991). The main characteristic features of the early stage of AA are an increase in the number of catagen and telogen follicles, inflammatory lymphocytic infiltrate in the peribulbar region (swarm of bees) and eosinophils in the stelae. The hair matrix is infiltrated by the lymphocytes and pigment, incontinence availability, matrix cell necrosis, and vacuolar damage (Wasserman et al. 2007). The inflammatory infiltrate is especially prominent in terminal hair follicles, the bulbs of which are located in the subcutaneous tissue. Peribulbar and intrabulbar lymphocytic inflammatory infiltrate resembling "swarm of bees" is a characteristic of histopathology (Peckham et al. 2011).

Hair follicles are going through two important morphological changes:

- Trichomalacia: short and incompletely keratinized "pencil point" hair that are susceptible to trauma, and
- miniaturization of some anagen follicles: the late stage of the disease is characterized by numerous miniaturized hair follicles, and telogen follicles are present (Wasserman et al. 2007).

AA as a disease related to loss of hair follicles, is an autoimmune disease, where the hair immune system is related to intrafollicular T lymphocytes, Langerhans cells, perifollicular mast cells and macrophages. AA is mainly related to the sensitization of T lymphocytes particularly
CD8+ T cells, and to other follicular antigens. Activation of the T lymphocytes that compose the perifollicular infiltrate are a characteristic of AA induced release of several Th1 cytokines - interleukin (IL)-1 alpha, IL-1 beta, and tumor necrosis factor (TNF) alpha. Those cytokines are capable of inhibiting hair follicle growth and arresting hair synthesis, with early termination of anagen (Hammerschmidt et al. 2014) (Figure 6).

There are two phenotypes of CD8+ T cells:

- Type I CD8+ cytotoxic T (Tc1) cells: they secrete IFN-γ, and kill tumor targets by either perforin or fast-mediated mechanisms.
- Type II CD8+ cytotoxic T (Tc2) cells: secrete IL-4 and IL-5. They kill tumor targets by using the perforin pathway (Ito 2013).

AA can also be related to a decreased number of CD4+, CD 25+ T regulatory cells (T reg). Treg function is modulated by the fork head box protein 3 (FOXP3) transcription factor and by Inducible Costimulator (ICOS), where single nucleotide polymorphisms in the promoter regions of FOXP3 and ICOSLG (ICOS ligand) genes can be associated with AA; so single nucleotide polymorphisms in the promoter regions of FOXP3 and ICOSLG genes are related to AA (Conteduca et al. 2014).

The major histocompatibility complex (HLA) is also associated with susceptibility to AA, where each gene is located on the short arm of chromosome 6 forming the major Histo-compatibility complex (MHC). The onset of AA is related to the up-regulation of MHC antigens, and also the change in regulation of locally produced immuno-suppressants (adrenocorticotropicin, melanocyte-stimulating hormone) where the immune privileged hair follicle antigens can be recognized by the immune system (Madani et al. 2000).

MHC class I and II molecules are not seen in healthy persons but with AA patients. The decreased immunosuppressive molecules with presence of adhesion molecules (ICAM-2 and ELAM-1) in the perivascular and peribulbar hair follicular epithelium lead to perifollicular inflammation and cause dystrophic hairs (Seetharam 2013).
HLA genetic system has many alleles. Alleles have different sequence of nucleotide bases. HLA is of two types or classes:

- Class I (A; B; C)
- Class II (HLA-DR, DQ, DP)

AA is mainly related to class II.

The main alleles are related to class II. There is an increase in HLA-DQB1*0301(DQ7) HLA-DQB1*03(DQ3) and HLA-DRB1*1104(DR11). The form HLA-DQB1*03(DQ3) appears to be a HLA marker of all forms of AA. HLA alleles DRB1*0401(DR4) and HLA-DQB1*0301(DQ7) are associated with AT/AU (Madani et al. 2000), while HLA-DQB1*0202, and DQA1*0501 are more related to AA, HLA-DRB1*1302 and DQB1*0604 with atopic dermatitis, and HLA-DQB1*03 and HLA-DRB1*04 to autoimmune hypothyroidism (Hashimoto thyroidism). HLA-DQB1*03 in general has a positive association with both AA and autoimmune hypothyroidism; HLA-DRB1*03 has a positive association with Grave disease and a negative association with AA (Barahmani et al. 2005, 2009).

AA, as mentioned above, can be associated with Th1 which involves IFN-gamma and IL-2, and with Th2 which involves IL-4 and IL-10; or it is associated with HLA class II (DQB1*0301, DQB1*0202, DRB1*1104, DQA1*0501). Others less associated are antibodies against hair follicle keratin, melanocytes, dermal papilla, IgE, mast cells and eosinophils. The severity of AA is associated with a polymorphism in interleukin 1 (IL-1) receptor antagonist gene, while atopic dermatitis is associated with Th1 which includes IFN-gamma (chronic), and with Th2 which includes IL-4 (acute). Other less associated are IgE auto-antibodies against keratinocytes, filaggrin (keratin cytoskeleton), IgE, histamine, mast cells and eosinophils (Barahmani et al. 2009, Whiting 2001).

In addition to HLA molecules, non-HLA molecules including the major histocompatibility complex class I chain-related gene A (MICA), a stress-inducible antigen, are seen also with several autoimmune diseases. The severity and occurrence of AA may be related to gene MICA (Barahmani et al. 2006). The class II MHC antigens are less frequently expressed in AA (Bröcker
et al. 1987). Carriers of IL-1B-511 CC genotype had an increased risk to develop severe AA; genotype CT is 50% less in severe cases of AA compared to semi-universalis, while genotype CC was 50% greater in severe cases of AU than others. Allele was significantly higher in severe cases (AU) but T cells where much lower in AU according to a study on patients in Kuwait (Alfadhli et al. 2012).

A recent study of Ito (2013) mentioned that the autoimmune response is initiated by the triggering of NKG2D receptors which are related to the UL 16-binding protein (ULBP3) gene cluster on Chromosome 6p25. Therefore, NK-activating ligands ULBP3, ULBP6 and other hair follicle genes like STX17, PRDX5, and the T cell genes like IL2/IL21, IL2RA, CTLA4, IKZF4, HLA are the most related genes for AA (Hordinsky 2011).

AA patients have increased NKG2D expression; KIR2DL2 and KIR2DL3 are significantly increased in AA patients compared with healthy controls. Marked pigment incontinence was observed in the dermal papilla, matrix, and CTS of hair affected follicles. The pigment incontinence may be due to the redistribution of numerous melanocytes and melanin that results from the immediate loss in the structural integrity of keratinocytes. At the center of the super-matrical zone in the upper bulbar area any melanophages and melanocytes were distributed in the dermal papilla and dermis around the lower follicles, also the connective tissue sheath (Lew et al. 2009). Other features are the presence of degenerative changes in the matrix, increased number of follicle stelae, incepted number of miniaturized vellus hair follicles, and pigment incontinence of hair bulbs and follicular stelae (Whiting 2001).

Decreased number of terminal anagen hair follicular stelae and vellus like hairs, are the main points in diagnosis of chronic cases of AA. Intrichotillonmania and other forms of traumatic alopecia such as traction alopecia, inflammation and miniaturized hairs are lacking but catagen hairs occur numerously. There is no inflammation in congenital triangular alopecia, loose anagen syndrome, or familial focal alopecia, but in the later a marked increase of telogen germinal units with no scarring indicates a telogen arrest. Cicatricial alopecia shows permanent destruction of follicles which are replaced by scare tissue (Whiting 2001).
In AA incognita, the loss of hairs occurred if all the anagen hair follicles of a lesion changed to dystrophic pointed roots leading to a bald surface. Smooth bald surface did not occur if the hairs in the involved area are of an increased number of telogen transformations. Bald patch is not formed in patients with a high percentage of telogen hair. Also hair thinning and AA is seen when there is increased telogen count in the circumscribed region. One of other characteristic features of the hair shafts of the telogen hair comparing to the anagen hairs of the normal surrounding areas are lighter color and thinner diameter (Park et al 2013).

The inflammatory infiltrate is especially prominent in terminal hair follicles, the bulbs of which are located in the subcutaneous tissue. Peribulbar and intrabulbar lymphocytic inflammatory infiltrate resembling "swarm of bees" is a characteristic of histopathology (Peckham et al 2011).

There are nanogen hairs that represent an intermediate stage between vellus and terminal anagen hair follicles. Inflammation may be absent in longstanding AA. Incomplete recovery way demonstrates a group of diminutive anagen follicles with large percentage of them showing the infiltrate. The number of melanocytes and overall melanization is decreased, which is partial or incomplete melanocyte activation in early anagen, in prolonged recovery stage, or if the disease remains chronic (Wasserman et al 2007). The immunosuppressive milieu of the anagen hair bulb modulated by immunosuppressive factors is known as “hair follicle immune privilege”, where the reduction of the hair follicle immune privilege will result in autoimmune reactions against hair follicle autoantigens (Madani et al. 2000).

**Figure (6):** Model of the pathogenesis of AA, where there is infiltration of anagen bulbs by T lymphocytes and antigen presenting cells, with premature reversion to telogen (Randall 2001)

T<sub>h</sub>=T helper lymphocytes; T<sub>c</sub>=T cytotoxic/suppressor lymphocytes.

●=dermal papilla.
Auto-antigens in hair follicle such as melanin associated proteins may be recognized by the accumulated auto reactive T cells and the chemokine. Chemokine receptor engagements are one of the most important points. Th1 associated as well as IFN-Y induced expression of CXCL9 and CXCL 10 is seen in AA. CXCL 10 expression is upregulated in skin lesions of acute phase AA. The T cell expressing CXCR3 (which is a receptor for CXCL 10) isolated from the patient have a high velocity toward CXCL 10, by promoting chemotaxis or CXCR3 +Th1 and Tc1 cells towards the cell bulb. Thus, both chemokine expression and T cell velocity induce "swarm of bees", and therefore the inhibition of T cell chemoattraction can be one of the most important and effective methods of treatment of AA (Ito et al. 2013, 2010).

A functional polymorphism in interleukin-1α (IL1A) gene is associated with risk of AA in Chinese populations as a potent inducer of hair loss and a significant human hair growth inhibitor. The 4-bp insertion/deletion (indel) polymorphism (r3783553) within the 3 untranslated regions of IL1A gene has been suggested to be associated with risk of various types of cancer, possibly through regulating expression of IL-1 α levels, so that the IL1A4-bp indel polymorphism may be a marker for genetic susceptibility to patchy (mild) AA in Chinese population likely through miR -122 mediated regulation (Lu et al. 2013).

The level of tumor necrosis factor alpha (TNF- α) mRNA is markedly decreased and the level of interleukin 1 receptor antagonist (IL-1ra) miRNA is increased in epidermal cells from early anagen to telogen in mice. Melanogenesis occurs during anagen, and melanin associated protein is strongly speculated to be hair follicle autoantigen, especially in AA pathogenesis. Anagen dependent immunosuppression is reasonable to decrease auto-activity during the anagen phase and conceals auto-antigen against auto-reactive T cells (Ito 2010). There is also a study showing that lymphoid specific protein tyrosine phosphatase, autoimmune regulator (AIRE) and nonspecific type 22(PTPN22) are immune-regulatory genes associated with AA (Betz et al. 2007, Tazi-Ahnini et al. 2002). Susceptibility alleles of genes encoding for cytokines and their receptors such as interleukin -1receptor antagonist (IL1RN) and chemokines (MCO-1) are also associated with AA (Barhamni et al 2002). Also the level of monocyte chemoattractant protein-1 (MCP-1) is elevated in scalp lesions of patients with AA (Hong et al. 2006). Genome
Wide association studies (GWAS) reported several susceptibility genes such as CTLA 4, SPATA5 and IL13 which are the most to be seen with AA (Lu et al. 2013). It has been found by this study that del/del, ins/del and ins/ins genotypes were significantly associated with AA in an allele dose response method, which can decrease the risk of AA (Lu et al. 2013). GWAS can be helpful for the explanation of pathology of AA and the choice of the drug that could be the best for the treatment of AA, depending on the mechanism of AA (Petukhova et al. 2010). In relation to AT it can be considered that the skin has a Th I cytokine pattern, with increased steady state mRNA levels for IFN-gamma, IL-I beta, and IL-2 after DPCP treatment. The IFN -gamma expression was reduced and IL-2, IL-8, IL-10 and TNF-alpha mRNA expression was increased (El Khory et al. 2013).

In a study with 71 cases, in 10 cases eosinophils were present. T lymphocytes express a variety of voltage-gated potassium channels (Kv) that greatly affect T cell function. Kv 1.3 channels regulate auto-reactive effector memory T cells which are related to AA as shown in Figure (7) (Gilhar et al. 2007).

![Figure (7): Comparison between normal and AA anagen follicle (Gilhar 2007)](image-url)
The histopathology of ADTA (acute diffuse and total alopecia) subtype of alopecia areata lesion revealed infiltration of mononuclear cells around the hair follicles and prominent pigment incontinence. Many melanophages and melanocytes were distributed in the dermal papilla and dermis around the lower follicles, also in the connective tissue sheath. Also IL-17 and IL-17F can be associated with AA (Lew et al. 2009, 2012). Marked pigment incontinence was observed in the dermal papilla, matrix and connective tissue sheath of hair affected follicles. The pigment incontinence may be due to the redistribution of numerous melanocytes and melanin that results from the immediate loss in the structural integrity of keratinocytes at the center of the supramatrical zone in the upper bulbar area (Lew et al. 2009). Some anagen hairs grow taper down proximally to pencil point because they are only partially damaged, incorrectly called anagen effluvium as in anagen arrest (Whiting 2001). The association of AA with both antibody-mediated (systemic lupus erythematosus and autoimmune thrombocytopenic purpura) and T cell-mediated autoimmune disease (Hashimoto thyroiditis and vitiligo) can be explained by the association of AA with both T helper 1 (Th1) and T helper 2 (Th2) cytokine response (Barahmani et al. 2009).

From all of above, T helper type 1 cytokines play an important role in the pathogenesis of AA (Willemsen et al. 2009, 2010). Therefore, AA is associated with other diseases like Graves' disease, vitiligo, diabetes, lupus erythematosus, pernicious anemia, rheumatoid arthritis, ulcerative colitis, Celia disease, Down syndrome, or immunodeficiency (Olsen et al. 2004).

### 3.4 Animal models for AA studies

Animal models are very important for understanding and developing treatments for disease in man. Dundee experimental bald rat (DEBR) and Smyth chickens are the most used animals in the laboratory for studies related to AA (Oliver et al 1991). Another important type is the severe combined immunodeficiency mice (SCID) model, where scalp explants from patients were transplanted to SCID mice and injected with autologous T lymphocytes which were isolated from involved scalp. T lymphocytes which had been cultured with hair follicle homogenate
along with antigen-presenting cells were capable of inducing the changes of AA (Gilhar et al 1998).

The **C3H/HeJ mouse** can spontaneously develop an adult-onset form of AA like disease that is very similar to human, where the most of studies depend on the investigation of the involvement of T cell activating molecules in the onset of AA (Sundberg et al 2011). AA can be induced in normal CH3/HeJ mice using full thickness skin grafts donated from the affected mice (Madani et al 2000). Its onset in mouse model C3H/HeJ can be reached by CTLA4-Ig, which leads to hair loss due to disease activation. One of the theories considered that CTLA4-Ig competes effectively with CD28 for CD80/CD86 preventing their interaction with CD28 and preventing the onset of AA, where CTLA-Ig can block the T cells. Other studies considered that the main immunologic changes that could be seen in the mouse model of AA are CD4 more than CD8, increase in IL-12, IL-6 more than IL-10, IL-4 and all T cells and shows also macrophages and B cells (Petukhova et al 2011). After depletion of either CD4+ or CD 8+ T cells AA model rats will develop complete hair regrowth (Ito et al. 2013). McElwee et al. (2003) showed that in a mouse model of AA the complex changes can be also represented by the presence of macrophages and B cells, and by an increase in IL-12, IL-6 more than IL10, IL-4 and all T cells. In all those types of mice the immunological AA is related to T lymphocytes in which auto-antigens are important to activate T cells that cause the disease. The leukocytes stimulated *in vitro* with hair follicle antigens and injected into the laboratory mice produce immunological hair loss similar to that in AA.

AA can also be in association with cardiac dysfunction in C3H/HeJ mice, those receiving adrenocorticotropic hormone (ACTH). Mice exhibit both arterial and ventricular hypertrophy and increased collagen deposition compared to normal haired littermates, and the heart of mice will be increased (Wang et al. 2013). AA in mice may develop with abnormal heart hypertrophy, where it is associated with elevation of *Il18*, *Col5a1* and cardiac remodeling marker cardiac troponin-I (cTnI). The production of *Il18* can be accentuated due to stress hormone like ACTH. This leads to damage in the heart and heart enlargement when compared with the healthy one, sham-grafted littermates. The density of cardiomyocytes nuclei in atria
and ventricles of AA mice is less in comparison to control. There is also an increased amount of collagen as a marker of cardiovascular disease which can cause heart failure. Also thinner blood vessel wall is seen because of collagen reorganization by cardiac fibroblasts, or due to reduction of the endothelial cell size (Wang et al. 2013). In graft-induced C3H/HeJ mice, an increase was observed in the gene which is related to the synthesis of retinoic acid in mice with AA. Also vitamin A is related to the severity of AA; less vitamin A fed for mice will increase the severity of the disease, and more hair follicles can grow in those mice fed with high levels of vitamin A (Amin et al. 2013).

Price et al. (2005) had suggested that AA may be due to one or several factors, and a virus infection could be one of the causes of AA, which needs more immunohistochemical and microscopical studies and investigations for clarification. The authors considered that AA is mainly related to chromosome 17 (Alaa1) and 9 (Alaa2). Additional markers in these intervals and saturation mapping purported intervals on chromosomes 8 and 15. Two new intervals, Alaa3 located in chromosome 8 and Alaa4 on chromosome 15, were identified (Sundberg et al. 2004).

Another gene related to AA in mouse is CLTA4, a co-stimulatory T-cell ligand that binds B7.1 (CD80) and B7.2 (CD86) on antigen-presenting cells. CLTA4 is primarily increased on CD4+/CD25−cells. CTLA4 (CD152) was found in the peripheral blood CD4+/CD25−cells of AA patients (see Sundberg et al. 2011). Mice show a deficit in habituation and stress due to elevation of cortisone and ACTH where stress receptors in the brain are altered. The release of cardiac troponin (cTnI) as a marker of heart tissue damage is due to the exposure to ACTH modulators (Wang et al. 2013).

4-SYMPTOMS OF ALOPECIA AREATA

The symptoms of AA as a non-scarring disease vary from one patient to another in its severity where hair loss is the most important symptom of AA, with a burning sensation or itching, pain and/or pruritus. The hair loss may be in one or multiple patches mainly on the scalp, bread,
eyebrows, eyelashes, arm or armpits, pubic region, or legs, or in ophiasis type, band like hair loss in parito-tempo-occipital area, and in ophiasis inversus (sisapho) very rare band-like hair loss in the fronto-parieto-temporal area. The patches are smooth and round in shape, they may be also mildly reddened or peachy in color. Hair follicles with exclamation points can also been seen at the edges of the bald patches. The presence of sparing white hairs can be easily seen in patients with gray hairs (AlKhalifa et al. 2010). The acute phase of AA is characterized by the whitening of hairs because in the anagen phase the hair will regrow in white or colorless within the patches of AA (Petukhova et al. 2011). At the border or within them the patches have characteristic exclamatory mark hairs; fractured and short hairs with proximal tapering can be seen. Nail abnormalities as a result of inflammation of nail matrix also can be seen in 10-66% of cases depending on the severity of the cases (Tosti et al. 2013).

There are also macrophages, and foreign body giant cells in the area of extensive inflammatory changes in inflammatory cells. Also inter- and intracellular edema can be seen because of inflammatory cells (Whiting 2001). Nails maybe yellow-gray colored and show severe onycholysis, involving the whole nail plate and nail bed hyperkeratosis (Kasumagic-Halilovic et al. 2011). There may be other nail features like pitting, trachyonychia, Beau's line, onychorrhexis, thinning or thickening, onychomadesis, koilonychia, punctuate or transverse leukonychia and red spotted lunula (Wasserman et al. 2007).

Below there is a comparison for the nails of patient before (Figure 8) and after (Figure 9) treatment with triamcinolone acetonide, where we can see the gray colored nails with hyperkeratosis in the first picture which returned almost to normal after 3 months of treatment.

**Figure (8):** Severe onycholysis with nail bed hyperkeratosis.  
**Figure (9):** After treatment with triamcinolone acetonide for 3 months.
5– CONCURRENCE OF AA WITH OTHER DISEASES

AA can be caused due to other diseases as a result of emotional stress especially with sex transmitted disease like Syphilis and HIV infection. In HIV patients there will be destruction of lymphocytes leading to the breaking of the tolerance for self- peptides causing the production of auto-reactive cytotoxic T cells. Those T cells respond to the cleavage products of apoptotic cells (Xuan et al. 2014). AA can begin as a diffuse alopecia (Lew 2009, Alkhalifa et al. 2010). The AA patients may be with a history of irritable bowel syndrome. The risk of having AA increased to 73% similar to 70% with atopic dermatitis and the risk of AA with hyperthyroidism increased 3 fold (Barahmani et al. 2003, 2005, 2009). AA can be also seen in pubis or upper thigh with pruritus without signs of inflammation with a negative pull test, and a negative history, where there is a dense, band like epiermotropic and folliculotropic lymphoid infiltrate, but no presence of follicular mucinosis (Iorizzo et al. 2010).

Systemic Lupus Erythematoses (SLE) can be associated with nonscaring patchy alopecia, where SLE can be distinguished by white dots, the thinning hair shaft, hypopigmentation of hairs, perifollicular red dots, angioepectasis, and honey comb pigment patterns, while AA is characterized by black dots and broken hair. The patches of SLE alopecia patients with AA have interfollicular polymorphous vessels as the most important feature, also local angioepectasis and vasculitis close to the hair follicle. In AA there will be inter-follicular arborizing vessels. Therefore, AA can be differentiated from SLE alopecia by serological autoantibody tests (Ye et al. 2013). AA can begin as a diffuse alopecia even it usually started with focal lesions of hair loss (Lew 2009). There may be confusion between the damage of some hair in trichomalacia and trichotillomania or traction alopecia (Whiting 2001). Yellow dots can be seen mainly because of the dilation of the affected follicular infundibulum with keratinous material or sebum, while the black dots are remnant of exclamation hair and broken hair (Ganjoo et al. 2013).

Iron deficiency may be also related to AA. In a study of Trost et al. (2006) with 106 females (18-70 years of age) the 17 with AA show a significantly decreased serum ferritin concentration compared with 11 female control subjects. The haemoglobin will not change. Also in a subgroup of 40 patients in young age (11 patients with AA and 6 controls) the same result has
been found. The main iron deficiency was seen in females more than men (Trost et al. 2006). AA could be seen also in a patient with chronic myelogenous leukemia when he was treated by transferring human leukocyte antigen-matched marrow from his brother who suffered from AA (Duvic 2003). Not only that but also other diseases are associated with AA such as increased risk of hypertension, hyperinsulinaemia, insulin resistance, metabolic syndrome, and having elevated serum total cholesterol and triglyceride levels. AA is associated with coronary heart disease and cardiovascular risk factors; the greater the severity of alopecia the greater is the risk of coronary heart disease (Trieu et al. 2014).

The incidence of thyroid disease can be increased with 8% - 11.8% in patients with AA, compared to 2% in normal patients, due to the increase of antithyroid antibodies and thyroid microsomal antibodies, while vitiligo increased 4 times in patients with AA (Madani et al. 2000).

AA also can be related to Down’s syndrome, Addison’s diseases, celiac disease. It was also found in a study from Seetharam (2013) that the children under 10 years old more often have atopic dermatitis or SLE than others, while psoriasis or rheumatoid arthritis are more frequently seen with patients in the second decade of age, and thyroid disease in old age.

AA can be seen or appeared after the infection by more than one diseases in the same patient, as an example for that is observed in a study from Xuan et al. (2014) in a young patient with immunodeficiency virus in China. After one month of anti-retroviral therapy, the patient's alopecia areata dramatically improved. The occurrence of AA and vitiligo in the same patient with AIDS happened due to the release of protein fragments from dying CD4+T cells that promote the formation of CD8+T cells in HIV infection; the patient's CD4 lymphocyte count and CD4/CD8 ratio were both so low.

AA and vitiligo have autoimmune basis. It can be considered that AA with thyroid disease and vitiligo are of high prevalence; also atopic reactions which are triggered by localized ‘hypersensitivity’ to an allergen/cross-reactive antigen (Tobin 2013). Vitiligo can be seen as white patches due to the destruction of melanocytes at any part of the body (Harris 2013). AA can be seen in patients with type 1 diabetes mellitus. Its risk can be increased in male patients. AA can be also seen in patient with vitiligo, thyroid diseases, and psoriasis (Chu et al. 2011).
There is also a thought that viral infection can evoke AA which causes an increase in interferons (IFN-γ) which leads to reduction in immune privilege (Ito et al. 2013).

Bhat et al. (2009) said that the AA patients show a decreased zinc level in blood and urine comparing to control, while the serum level of copper and magnesium are not changed.

AA can be related with malignancy which has been explained in a study from Shin et al. (2012) in 3 cases of lymphoma, alveolar part sarcoma, and cavernous sinus arteriovenous fistula that can occur with rectangular patterned occipital AA. Alopecia neoplastica is caused by the cutaneous infiltration of malignant cells from a distant malignancy, and is characterized by single or multiple patches, or nodules. Alopecia neoplasia is associated to other diseases like breast cancer, cervical cancer, gastric and adenocarcinoma, melanoma, lymphoma, etc. Alopecia neoplastica has been reported also to mimic AA, and discoid lupus (Kirby et al. 2010).

Another cause of AA can be also therapeutical. As an example for that AA occurred as a result of using adalimumab in patients suffering from pustulosis palmoplantaritis. In this case AA developed due to dysregulation of immune responses due to TNF-α blockage (He et al. 2012).

A study by Campuzano–Maya (2011) shows that AA can be cured also in patients with stomach ulcer after the eradication of Helicobacter pylori in a male patient of 43 years with 8 months history of AA. AA can be less associated with schizophrenia in comparison with other psychiatric diseases. It is also related to anxiety and alexithymia especially in children. This association between AA and anxiety is mainly in age between 20 and 39, and the use of hypnotics will be therefore helpful to reduce anxiety (Ghanizadeh et al. 2014).

Two diseases can be seen in the same area or location, where AA can be present with psoriasis where psoriasis appeared inside the patches of AA. Psoriasis changed after remission to AA and then reappearance of psoriasis during the hair growth, which means rapid change from Th-1 to Th-17 and then back again to Th-1. Psoriasis (Th-17) and AA (Th-1) are mainly related to T cells. The Renbök phenomenon is the name of AA which is seen in patients who have also psoriasis, where this disease is related to the T cells. AA and psoriasis cannot occur at the same site.
because each inflammatory pathway increases its own response and inhibits opposing pathways (Ovcharenko et al. 2013).

**Syphilis** can cause AA or vitiligo because the patient had suffered of a bad psychological situation. Vitiligo is a depigmentation disease due to destruction of melanocytes in the epidermis. The patients with vitiligo show an increase in the CD8+/CD4+ ratio, where the inflammatory cells CD8+/CD4+ are prominent in the perilesional areas. Xuan et al. (2014) said that syphilis infection can cause AA or vitiligo like lesions. AA risk increased in those patients having a history of atopic dermatitis and the risk is 3 times greater for AT and AU (Barahmni et al. 2009).

**Nitric oxide** can induce damage in erythrocyte superoxide dismutase (eSOD) which results in NO-eSOD that is of greater extent in patients with AU, a high level of NO or carbonyl contents, and also shows a lower level of SOD activity as compared with other AA patchy persistent. Therefore, the neo-epitopes are related strongly to AA where the eSOD is considered as a risk factor as approximant in AA patients (Rasheed et al. 2014).

**6- CAUSES OF ALOPECIA AREATA**

The etiology of AA is a continuing revolution since 1760, where AA was reported to be due to the parasitic or infectious etiology between the children in schools and orphanages especially in the 19th and 20th centuries, or it may be related to emotional or physical stress, trauma, vaccination, foods rich in soy oil, cytomegalovirus infections and hepatitis B vaccination; and there was an increased level of Zinc observed in the blood of patients with AA (Seetharam et al 2013).

AA is related to **genetic, immunological and psychological causes**. There is no evidence that AA follows the Mandel’s law, but the immunological one is mainly related to HLA class II loci, TNF and genes mainly at chromosome 10, 6, 16 and 18 (Lenane et al. 2005).
AA is considered as a state of kenogen because the hair follicle becomes empty showing that AA can occur before the anagen starts. Genome wide association studies (GWAS) identified specific genes in AA related T cells (IL2/IL21, IL2RA, CTLA4, IKZF4, HLA) and hair follicle (NK-activating ligands-ULBP 3, ULBP6, STX17, PRDX5) (Seetharam et al 2013). The DNA restriction polymorphism of MHC class II genes HLA-DQA, -DQB, -DPA, and -DPB was investigated in 20 Danish patients with AA and in healthy Danes. The frequency in AA of the DQB1*0301 and DQw7 associated DQB Bgl/II 4.2 kb fragment was increased to 65.0 % compared to 23.2 % in controls suggesting that the previously reported associations between AA and both DR4 and DR5 is secondary to an association between AA and DQB1*0301, which codes for the beta-chain of the HLA-DQ molecule of the serologically defined HLA-DQw7 specificity. Individuals who carried both DQA1*0501 and DQB1*0301 seemed to have a further increased risk of developing AA compared to individuals carrying only one of these HLA class II genes. Analysis of the combined presence of DQB1*0301 and DPA1*0103 in AA suggests that an additive risk effect exists between the DQB1*0301 and DPA1*0103 alleles which are situated at different HLA class II loci (Morling et al. 1991).

Price et al. (2005) considered that pigmented hairs can fall while the not pigmented or white hairs appeared in those patches of AA, where the new hair follicles are often not pigmented. The major histocompatibility complex (HLA) is associated with susceptibility to AA, as well as other autoimmune diseases. In addition to HLA molecules, non-HLA molecules including the major histocompatibility complex class I chain-related gene A (MICA), a stress-inducible antigen, are also associated with several autoimmune diseases. MICA(6) was significantly associated with all phenotypes of AA, whereas MICA(5.1) was significantly associated with patchy AA. Extended haplotype analysis showed the significant associations of haplotypes HLA-DQ1-DR6-MICA(*)5.1 and HLA-DQB1*0201-DR3-MICA(*)5.1 with AA. These results suggest that MICA is both a potential candidate gene and part of an extended HLA haplotype that may contribute to susceptibility to and severity of AA (Barahmani et al. 2006).

As a result of above the extent of hair loss is related to the ratio of CD+4 and CD+8 of the inflammatory infiltrate; the increase of hair loss means the increase in this ratio. AA can also be
described by high rates of antibodies, increase in the prevalence of antithyroid and antinuclear antibodies, and also gastric parietal cell antibodies (Friedmann 1981).

Vitiligo as an autoimmune disease has a strong relationship to AA. AA and vitiligo have the same autoimmune basis (Tobin 2014). AA can be also seen in patients with type 1 diabetes mellitus, where the effect of IL-1 and IL-1B multiplies by IL-1 receptor antagonist or cAMP pathway inhibitors. IL-2, IFNγ, IL-5, and IL-16 are also related to AA. Therefore, the cytokines abnormalities and the increased CD8/CD4 ratio explain that AA is an autoimmune disease (Wasserman et al. 2007). Vitiligo is represented by white patches on any part of the body due to the destruction of melanocytes. AA and vitiligo differ in the method of treatment; both are of genetic risk factors; diphenylcyclopropenone (DPCP) is not effective for vitiligo (Harris et al. 2013).

Gilhar et al. (2013) reported that the autoreactive effector memory Tcells can be regulated by a number of voltage-gated potassium channels (Kv) which are present on T lymphocytes. Kv1.3 containing cells are mainly found by using Double-immunofluorescence confocal microscopy. This theory can be of benefit for the treatment of AA by blocking these channels using 5-(4-phenoxybutoxy)psoralen (PAP-1) which is a selective small-molecule blocker of Kv1.3, and it inhibits the proliferation of human CCR7−T cells.

AA can be also associated to Lymphoid-specific protein tyrosine phosphatase, non-receptor type 22 (PTPN22), which is an immuno-regulatory gene associated with AA. PTPN22 1858C>T mutant genotypes are related to the longer duration of the disease reflecting the early age of onset. There is a significant association of PTPN22 1858C>T polymorphism with severe cases of AA; however there is no effect of this polymorphism on the response or resistance to DPC therapy in 103 patients treated with DPCP. Also PTPN22 CT and TT are higher in AA patients. The presence of harboring mutant genotypes will cause the delay of treatment (El-Zawahry et al. 2013). Another study from Hordinsky (2013) suggested that the higher level of ULBP3 in the hair follicles is a good marker of AA.

The significant target antigen in diverse autoimmune diseases is the high mobility group box 1 protein (HMGB1) which is released by necrotic cells and in response to various inflammatory
stimuli. The level of this antigen is higher in AA patients. Therefore, it is considered to be important in the etiology and treatment of AA (Lee et al. 2013).

In a report from Xuan et al. (2014) a case of a patient suffering from Aids with vitiligo and AA is described, because of chronic immune activation and progressive immune exhaustion in HIV infection in relation to the generation and maintenance of CD8+T cells. AA as an autoimmune disease can be induced by the inhibition or collapse of hair follicles immune privilege (Ito 2010). There is no well-known cause of AA till now (Whiting 2000).

**The genetic predisposition and autoimmune process are the main causes of AA.** There are also other causes like stress which may be related to other dermatological diseases, where the patients show a high 24 h urinary excretion of catecholamine, and also psychological situations like anxiety and depression (Díaz-Atienza et al. 2011). Those are seen before the occurrence of AA represented by the loss of hair, loss of social sport, especially for children and adolescents (Picardi et al. 2001). Due to iron deficiency, patients who take food rich with soya oil suffer less from AA. Low levels of zinc in the blood can be also seen in patients with AA (Seetharam et al 2013). It can be considered that 20%-30% of patients of the general population have a family history of AA. That means it can be an inherited disease (Lew 2009). AA is related to the genetic factors in 10-42% of cases. 37% have a first patch with 30 years of age, and 7.1% before 30 years of age; 55% of cases are also for twins (Madani et al. 2000). CD8+ [T cell](#), CD4+ [T cells](#) and [NKG2D+ NK or NKT cells](#) and the exact role of genetic factors in AA pathogenesis need more investigation (McElwee et al 2013). Other causes related to AA include seasonal variation, infections, vaccine, or desensitizing injections and emotional stress (Whiting 2000, Petukhova et al. 2011). Cytokines may be the cause of the onset of AA or damage for the hair follicle (Tobin, 2013).

**The severity of AA is higher when there is reduction of T cells.** The increase of CD4 and decrease of CD8, resulting in an increase of the ratio of helper to suppressor cells, are related to the severity of AA. In summary, T helper cells produce 2 types of cytokines, IFN-Y from type 1 T helper cells (Th 1), and Th2 produce IL-4 and IL-5, which derive from keratinocytes. The potent inhibitors of the growth of hair follicles are IL-1α and IL-1B and TNF-α. Also there is a decrease
in the expression of calcitonin gene related peptide (CGRP) which has an anti-inflammatory action (Amin et al. 2013). GWAS study shows that the genes CTLA4, IL2/IL2RA, IL21 are associated with autoimmune diseases like type 1 diabetes, SLE, Crohn's disease, multiple sclerosis and psoriasis, while NKG2D receptor association gene is related to rheumatoid arthritis, Crohn's disease, celiac and type 1 diabetes (Petkhova et al. 2011). There are other causes of AA related to the physiology of hair follicles, where the disturbances in blood supply for the hair follicles are related to AA. After DPCP therapy the capillary vessels number can increase due to increase of the vascular endothelial growth factor (Gerkowicz et al. 2013).

Varicella Zoster Virus infection can trigger AA, where active viral replication occurs in epidermal keratinocytes, causing intraepidermal acantholysis and vesiculation. AA can also occur after chickenpox (El Hayderi et al. 2012).

Another important factor related to AA are chemokines, where the expression of Th1 chemokines CXCL9/MIG and CXCL10/IP-10 increased in AA lesions, also serum CXCL9 level is correlated with disease activity (Ito et al. 2013).

Lee et al. (2013) considered in a study on 45 patients with AA of different age with 10 health control subjects that AA increased with increase of a protein located in all mammalian nuclei named high mobility group box 1, as compared to the control subjects. A study from Dubois et al. (2010) show that AA impairs quality of life by altering social life and mental comfort, which are more affected in AA than in neurofibromatosis.

GWAS for AA explained the relation of genes with 8 regions in genom. The genetic markers are identified by the existence of alleles which are related to the existence of AA (Petukhova et al. 2011). GWAS identify Linkage Disequilibrium (LD) blocks which are smaller segments of a size (20-50 kb) which contain one or few genes across the genome. There are 500,000-1 million genetic markers enabling the presence of a single polypeptide on the genome called a single nucleotide polymorphism (SNPs). It is shown that CTLA4 is associated with many autoimmune diseases like diabetes mellitus, and lupus erythematosus. The co-stimulatory locus resides on the chromosome 2q33 that is related to AA. It is comprised of a -300 kb region and it involves 3
types of genes which are: CD 28 (appears on T cell), CTLA24 and ICOS. Those genes display after T cell activation as a sequential gene duplication event (Petukhova et al. 2011).

There are other chromosomes that are related to AA which is chromosome 4q27 (IL2/IL21) and chromosome 6p21.32. HLA class II is mainly related to AA, also the most SNPs are rs9275572 and rs11752643. AA can be also related to genes on the chromosome 6q25.1 (ULBP6/ULBP3). NKG2DL include both MICA/B genes and ULBPs (considered as a stress induced molecule), which alert NK and CD8+T lymphocytes (Petukhova et al. 2011).

Chromosome 10p15.1 (IL2RA): GWAS study show that IL2RA (CD25) gene, located on this Chromosome, is related to AA pathogenesis. It is associated also with other diseases like vitiligo, Crohn's disease, Diabetes mellitus, and rheumatoid arthritis.

Chromosome 11q13 (PRDX5): PRDX5 is (peroxiredoxins) can be related to cellular stress. Cell stress causes the induction of PRDX, which is a family of enzymes that convert H₂O₂ into a harmless product. For that reason the dysregulation of PRDX5 develops autoimmunity; also this gene is related to other diseases like SLE.

Chromosome 12q13 (Eos/ERBB3): is not associated with AA, but mainly with type I diabetes; this gene can be also related to Treg development. EOS is considered as a critical mediator for FOXP3 dependent gene silence in Tregs, where the chromatin modifications cause immunity suppression due to interaction of EOS directly to FOXP3.

AA acute stage shows also an increase in the antigen MAGE-A3-reactive CD8+ T-cells, where CD8+CTLs react with melanocytes associated proteins (MAGE-A3) in HLA-A2402+ AA patients. AA can be induced also by the triggering of the CTL attack on the hair follicles because of the ectopic MAGE-A3 expression (Ito et al. 2013).

The non-scarring alopecia (acute diffuse and total alopecia areata, ADTA, and alopecia totalis, AT) ADTA can completely recover. Sisiaphoas is an unusual form of alopecia, which is difficult to differentiate from frontal fibrosing alopecia. In trichotillomania the hairs remain in the anagen phase. The scarring alopecia is described by hair loss of follicular ostia or atrophy, which can be histologically confirmed and inflammation may occur frequently (Amin et al. 2013).
AA as an inherited disease can occur also in **monozygotic twins**. The candidate gene studies show that the following genes show the most association to genes in HLA region: HLA-DQB1, HLA-DRB1, HLA-A, HLA-B, HLA-C, NOTCH4, and MICA. The relation between AA and MHC region on chromosome 6P is confirmed by genome wide scan, and also the loci on chromosomes 10, 16, 18, while the GWAS found keys related to T cells (IL2/IL21, IL2RA, CTLA4, IKZF4, HLA) and hair follicle (NK-activating ligands-ULBP3, ULBP6, STX17, PRDX5) (Galan-Guttierrenz et al. 2009, Seetharam 2013).

### 7- DIAGNOSIS OF ALOPECIA AREATA

The determination of hair loss percentage can be achieved by one or more than one investigators. The main method is either to visually control the hair regrowth or by dividing the scalp theoretically into 4 quadrants, and counting then the percentage of scalp surface. The percentage of hair loss can be determined and multiplied by the total scalp and delineated by that quadrant, and finally adding the result for each quadrant. AT determined as 100% is terminal scalp hair loss without any body hair loss, while AU is 100% of terminal scalp hair and body hair loss (Olsen 1999).

**Methods for the diagnosis of AA:**

- **Trichoscopy** (a noninvasive, very useful, easy and modern painless test method)
- **Hair-pull test**
- **Trichogram**

AA can be determined by **histopathological examination** when the diagnosis is uncertain; also it needs just experience of the operator with no need of hair shaving or dying; images can be recorded (Brzezińska-Wcisło et al. 2014). AA findings made by 4 mm punch biopsy in to 2 specimen, one vertically and the other horizontally sectioned, is more often used for the diagnosis of AA. Vertical one can certify the result. When there is less than 1 follicle/mm² it means less possibility for hair growth (Seetharam et al. 2013, Manjot et al. 2014).
The main related diagnostic features are black dots, yellow dots, short vellus hair, broken hairs and tapering hair; yellow, pink, round or polycyclic dots of different size of the same intensity of color or of uniform color (Hegde et al. 2013). The following figures (Figures 9-14) explain the appearance of all the types of dots whether they are black, yellow, with the broken hairs, vellus or with tapering hairs.

**Figure (9):** Yellow dots

**Figure (10):** Black dots

**Figure (11):** Broken hairs

**Figure (12):** Short vellus hairs

**Figure (13):** Tapering hairs

**Figure (14):** Yellow and black dots with broken and tapering hair through Dermoscopy.

(Seetharam 2013)
Another modern technique is the **videocapillaroscopy** using an optical fiber probe which is connected to microvideotelecamera with a 200 times magnification power in order to achieve the morphological and functional analysis of microcirculation. It can be used also for the nail fold where the capillary loops can be detected. The microvascular abnormalities of AA can be determined by the presence of abnormal videocapillaroscopic images.

**Dermoscopy** is one of the most important methods for diagnosis of AA, used at a magnification of ×25 and ×60. Also the use of video dermoscopy with a magnification of 20-70 times may be valuable (Alkhalifa et al. 2010). The dermatoscopic finding was black dots in 84% of cases, yellow dots in 57.33%, broken hairs in 37.33%, short yellow hair in 68% and tapering hair in 18.67% of cases (Hegde et al. 2013).

The use of videodermoscope is a non contact diagnosis and done with lenses ranging from ×20 to ×1000 magnification, which include 3 methods: the white light, ultraviolet (UV) light and the polarized light (PL), while alcohol or oil as an interface solution can be used for contact diagnosis (Jain et al. 2013). A study considered that the blood test and scalp biopsy are the most often used ways to check the presence of AA (Ganjoo et al. 2013). Other studies said that Lupus and secondary syphilis require serology testing or a scalp biopsy for confirmation and differentiation from AA (Alkhalifa et al. 2010).

In general trichoscopy or dermoscopy is a non-invasive method of hair and scalp evaluation and based on study of follicular patterns, interfollicular patterns and hair signs (Jain et al. 2013). Trichoscopy is described as a simple and noninvasive technique for diagnosis of AA, and for the evaluation of the treatment response photographically. It also can be used for diagnosis of other diseases like androgenic alopecia, telogen effluvium, tinea capitis, trichotillomania, lichen planopilaris, discoid lupus erythematosus and hair shaft disorders (Jain et al. 2013, Amin et al. 2013, Seetharam 2013). The follicular accounts with horizontal sections are particularly more effective in the diagnosis of AA when the biopsy is taken between acute episodes, and the characteristic peribulbar inflammatory infiltrate is absent (Whiting 2001). The best place for taking a biopsy is the active characteristic peribulba and inflammatory infiltrate in both horizontal and vertical sections, where the main diagnostic feature of AA is the decreased
terminal anagen and increased terminal catagen and telogen hairs, follicular stelae, and high or miniaturized vellus hairs. Also there is higher telogen percentage than in other diseases (Whiting 2001).

A study from Mane et al. (2011) described the dermoscopical method for diagnosing AA. It is considered that the type and the severity of AA is not related to the dermoscopical findings, where Hans HNS-50NP dermoscope model with magnification of ×32 and ×140 has been used with 66 patients of 25.5 years onset of AA and with a duration of 10.3 months. It showed that the most dots were yellow ones which were seen in 81.1% of the patients, while 66.6% of them having black dots, 55.4% having broken hair, short vellus hair 40.9% and tapering hairs 12.1%.

**The following tests are the mostly used for the diagnosis of AA:**

1-**The pull test:** It is used for the evaluation of the diffuse hair loss of the scalp by counting the number of hairs under microscope by a gentle traction exerted on a group of hair (about 40-60) on three different areas of the scalp. From the hairs per area more than 6 hairs are pulled out by the root after gently but firmly tugging on a small clump (about 60 hairs). AA shows positive test in contrast to androgenic alopecia and trichotillomania; those are giving negative results (Dombrowski et al. 2005).

2-**The pluck test:** Determination of the phase of hair growth. Telogen hairs are hairs having tiny bulbs at their root, telogen effluvium is represented by increased hairs, and anagen effluvium is represented by decreased telogen hairs with increase in the number of broken hairs. Diffuse AA can be easily misdiagnosed as telogen effluvium.

3-**Scalp biopsy:** Hairs around the bald patches are used to distinguish between scarring and nonscarring form, especially when it cannot be clinically differentiated. Biopsy specimens from the patients show a dermal infiltrate, mainly eosinophilic with perivascular localization (Maitland et al. 1984).

4-**Daily hair counts:** The hairs are counted from the first morning in a plastic bag for 114 days. The hair fall of more than 100/day is abnormal, with shampoos it will be up to 250 as normal
case (Amin et al. 2010, Seetharam 2013). The diagnosis of AA is improved by the use of horizontal section in addition to or instead of vertical section of scalp biopsies (Whiting 2001).

Diagnosis of ADTA can be made by a serologic test including anemia test, VDRL, antinuclear antibodies, thyroid function test and hormones such as testosterone, estradiol, luteinizing hormone, and follicular stimulating hormone. The hair pull test at each bilateral point of the frontal, temporal, occipital and parietal portions in patients is performed on 6 mm scalp biopsy specimen that are to be taken from the active or recent hair loss areas (Lew 2009).

AA can be diagnosed by the use of electron microscopy with a magnification power of 10 times, and by examination of microdissected hair follicles from scalps showing ultrastructural abnormalities in the dermal papillae represented by a prominent expression of ICAM-1 in the dermal papilla and keratinocytes of the matrix and outer root sheath (Madani et al. 2000). In general the diagnosis methods of AA can be also classified as invasive (biopsy), semi invasive (trichogram) or non-invasive (hair count, weighing shed hair and pull test) (Jain et al. 2013).

AA is very difficult to be distinguished from syphilitic alopecia. Syphilitic alopecia is characterized by the presence of plasma cells with few or without peribulbar eosinophils and abundant lymphocytes in the isthmus or peribulbar area. AA can be also distinguished from androgenic alopecia where the lack of lymphoid infiltration at the level of infundibulum and pigment incontinence within fibrous tract is the main feature of androgenic alopecia. While AA can be also differentiated from telogen effluvium which is characterized by normal number of hair follicles with no miniaturization of follicles and a slight decrease in the anagen/telogen ratio, trichotillomania is represented by empty anagen follicles, multiple catagen hairs, trichomalacia and pigment casts in the follicular infundibulum (Madani et al. 2000).

Severe types of alopecia are represented with white dots in interfollicual epidermis. It can be also interspersed with ducts openings as well-defined regularly placed hypopigmented dots. Also black dots can be seen with yellow dots. Polarized alopecia can be described with colored round or polycyclic dots. It is represented with follicular infundibulum which is distended with degeneration of keratinocytes and sebum. Yellow dots are seen in androgenetic alopecia, female androgenetic alopecia and trichotillomania, although some studies show that the number of
yellow dots are limited in AA (Gonjoo et al. 2013). One of the advantages of follicular accounts is in diagnosis of AU and in patients over 60 years where AU is described by a marked drop in follicular account (Whiting 2001).

The main differentiation and diagnostic features of AA from other diseases are mentioned in the following diagram (Chart 1).
Other tests used for diagnosis of AA are:

-The Purified protein derivative (PPD) test, which will be positive in patients with AA (Farshi et al. 2008).

-Complete Blood Test (CBC): prothrombin time (PT), partial thromboplastin time (PTT), erythrocyte sedimentation rate (ESR), blood urea nitrogen (BUN), creatine (Cr).

-Liver function test (LFT), thyroid function tests (TFT), and chest X ray are also used for the diagnosis of effectiveness of drugs used in the treatment of AA such as azathioprine (Farshi et al. 2008, Amin et al. 2013).

8- REACTIONS TO AA IN CONTACT WITH SURROUNDING EFFECTS

The patients who suffer from AA mainly have stress because of their situation which may develop to a more complicated psychological situation. AA is considered as a challenge for those patients and also for their family. Therefore, the patients should overcome this psychological and emotional stress. One of the most important ways of psychological therapy to improve their emotional situation will be reached when they meet other people who suffer from the same disease. There are a lot of psychological reactions in relation to the disease like depression, sadness, lonely feelings, hopelessness, embarrassment and angry. These symptoms are seen mostly in children and in the young because they have fear that the other may discover their disease and have shame from it, or they have fear that the parents or the other members of the family may be a part of the disease because they have the feeling that this disease is an inherited disease. Therefore, it is important for the patient to visit a physician or a clinic in order to treat the disease and to get more power and encouragement to overcome the bad emotional situation. There are supporting groups in some medical health centers or hospitals to help those patients during their therapy period and to support them as much as possible, and to make them not feel lonely. There are other ways to overcome this situation by changing the routine of life and to find the safe and best area for living (Willemsen et al. 2010).
Those patients living in stress due to their family situation or the community and work, or due to stress during study can show a higher 24-h urinary excretion of catecholamine. AA patients are more likely to be seen in the member of the family especially of one parent, where it is thought that there is a relation between the disease and genetics (Diaz-Atienza et al. 2011).

AA has 4 stages, those stages are: Acute hair loss, persistent alopecia, partial telogen to anagen conversion, and recovery. Inflammatory cellular infiltrate which is a peribulbar lymphocytic infiltrate (Swam of bees), consists of T lymphocytes, macrophages and Langerhans cells; also eosinophils are present in all stages of the disease. Therefore, it is considered as a diagnostic character for AA. The acute phase of AA is described by the formation of dysplastic hair shafts with failure of matrix cells and metrical melanocyte. The telogen stage begins after the complete matrix failure with increase in the telogen catagen hairs can be seen in the horizontal section of scalp biopsy specimen. When the patients suffer from long standing AA, then there is an increase in the number of Langerhans cells with peribulbar infiltration, and reduction of the follicles with decreased follicular density (Madani et al. 2000).

9- PROGNOSIS OF ALOPECIA AREATA

The most prognosis factors of AA include the type of the disease (AA, AT, AU), extent of hair loss, duration of hair loss, age of onset, family history, and nail changes (Lew et al. 2009). The risk of AA is 2 fold with those patients suffering from atopic dermatitis, one of the most diseases associated with AA, and at a risk of 3 times greater for those with AT and AU (Barahmni et al. 2009). These can worsen the patient situation and complicate the healing or delay of it, especially the association with atopic dermatitis. In long standing AA, follicles shrink greatly and pass through abnormal growth cycles reverting to telogen on reaching early anagen (growth phase) (Tobin 2013). AA can be related to DM type I with an increased risk of multiple comorbidities; also the diagnosis depends on the onset of AA and age of the patients (Chu et al. 2011).
The severity of AA and its activity is represented by the presence of broken or destroyed hair; cadaverized hair is a characteristic hair for AA patients where it can be defined as a broken hair with fractured tips, and can be fractured before emergency of the scalp, or as a short twisted dystrophic hair, vellus hairs seen after treatment or as a result from hair regrowth spontaneously. Those vellus are more detected in Asians because of the dark skin of patients (Gangoo et al. 2013).

10-TREATMENT METHODS OF ALOPECIA AREATA

Treatment is usually only done by a skin specialist and referral to hospital will usually be needed. Treatment of AA mostly depends on the decision of the physician to be treated or not. AA can remove spontaneously without treatment in many patients, other patients need therapy. Some treatments may be of benefit just for a period of time and the disease may return (Torchia et al. 2010, Pektukhova et al. 2011). Therefore, the treatment depends on several points which are so important in order to get good results.

1/ Situation of the patient and the degree of the severity of AA (AT/AU); its association with other diseases should be also taken in consideration if the same patients suffer from other diseases.

2/ Side effects of the drugs, their interactions with other drugs and contraindications should be considered.

The treatment of AA may take a long time which is not less than 3 months or more in some cases till there is a good and accepted hair regrowth. In most cases there is need for the combination therapy. The entire scalp needs urgent therapy or to be left as control to be provided as an indication whether the treatment should be continued. Some methods of treatment can begin with use of one drug with low side effects, then use of another drug or more, depending on a lot of points. One of those points considered as the most important one is the severity of the disease (Galan Gutierrez 2009).
It is important to say that in most studies the initial hair regrowth, whether spontaneous or induced by treatment, is typically none- or hypo-pigmented; but the color of hairs can usually return spontaneously to the normal color with time (AlKhalifa et al. 2010). AA is often resistant to several treatments, and recurrence can be seen. Therefore, it is not so easy to treat AA. The pain associated with concomitant muscle contraction can be treated with Botulinum Toxin Type A injection (Cho et al. 2010). The frequency of AA treatment depends on the progressive disease severity. AT is more difficult to treat; it needs a long time therapy and it may be expensive for the patients (Mukherjee et al. 2009).

AA can be considered as one of the most complicated diseases where it may be present with other diseases in the same patient and the same place on a distinct place on the body. There is a need for the evaluation of efficacy with a sufficient power and with statistical significance, where the evaluation of the efficacy can be influenced by the reduction or lack of the patients, even though there are good treatments for AA alone or with AT and AU. There is no standard guideline for the treatment of AA except that explained by one of the past ideas for the treatment of AA showing the use of 3 (minoxidil, diazoxide, and pinacidil) drugs acting as potassium channel openers which increase the hair regrowth by modulating the hair cycle (Price et al. 2005, 2008).

10.1 Main lines for treatment of AA:

There are several treatment options proposed:

2-Line therapy:

- First line treatment: Intralesional or topical corticosteroids or topical immunotherapy
- Second-line therapies: topical minoxidil, anthralin, and phototherapy with psoralen plus near ultraviolet light (UVA) therapy or systemic treatment with oral glucocorticoids, sulfasalazine, cyclosporine, methotrexate or use of a combination therapy of more than one drug (Hordinsky 2013)
Other suggested drugs for AA which can be used for treatment of AA: topical bexarotene, fractional photothermolysis, and topical bexarotene. Topical tacrolimus is under trials for the treatment of AA in humans (Bajaj et al 2008)

3-Line therapy:

In studies from Alsantali (2011, 2013) he explained a new plan for the treatment of AA depending on the age of the patient and extent or severity of the disease. The therapies of AA can be organized depending on their efficacy and safety into 3 lines:

- Intralesional corticosteroids, topical corticosteroids, minoxidil, anthralin, topical immunotherapy, prostaglandin analogs, topical retinoid, bexartone, and capsaicin.
- Sulfasalazine, photochemotherapy, excimer laser, fractional photothermolysis laser.
- Systemic corticosteroids, methotrexate, cyclosporine, azathioprine, biologics, physiologic support.

Other effective drugs and also foods were described for the treatment of AA like: aromapathy, a combination of topical garlic gel and betamethasone valerate cream, topical azelic acid, oral zinc supplementation, topical onion juice, and candida antigen. These applications need to be confirmed studies in large scale, double blind, and placebo controlled trials. Other treatment options are: photodynamic therapy, topical 5-flurouracil, topical tri-iodothyronine ointment, imiquimod, topical calcineurin inhibitors and botulinum toxin type A.

4-Line therapy:

- First line therapies include intralesional triamcinolone acetonide injections (2.5–10 mg/ml, in a maximum volume of 3 ml for each single injection, repeated at 4–6 weekly intervals by the use of mesotherapy multi-injectors, with topical steroids, minoxidil, anthralin, topical immunotherapy, prostaglandin analogues, topical retinoids and capsaicin.
Second line of therapy involves the use of oral sulfasalazine of 500 mg 2 times a day at first, then increase in the dose to 1 g 2 times daily for 1 months, then 1 g 3 times for 3 months, with the use of PUVA, PUVA-turban, excimer laser and fractional photothermolysis laser.

The 3rd line of therapy includes systemic steroids, methotrexate 15–25 mg/weekly for 3 months, cyclosporine, azathioprine, biologics and psychological therapy. There are also other types of therapy like garlic gel, azelaic acid, topical onion juice, imiquimod, calcineurin inhibitors, botulinum toxin and photodynamic therapy.

5-Line therapy:

Sardesai et al. (2012) said that there are 5 regimes for the treatment of AA when there are more than 5 patches and more than 25% of the scalp is diagnosed as AA, those 5 regimes are:

- Regime I: Intrallesional Steroid (Inj. triamcinolone acetonide 10 mg/ml), intrallesional injection of 0.1 ml/cm² once monthly is applied to get more effect by passing the barrier zone; although there will be hyper- or hypopigmentation, anaphylaxis and hemorrhage at the site of application; this regime shows few side effects like headache.
- Regime II: Topical Steroid (betamethasone dipropionate 0.05% lotion) applied twice daily
- Regime III: Minoxidil 5% lotion applied twice daily.
- Regime IV: Anthralin (1.15% + salicylic acid 1.15% + coal tar 5.3% ointment). Short contact therapy once daily, initially for 30 min. and gradually increased to 1-hr application.
- Regime V: placebo therapy (propylene glycol).

One of the best methods is the combination therapy which shows a good response represented by the regrowth of hair in a period of 3 months are regime I followed by regime 4. Minoxidil showed no results, just like placebo in some patients (Tobin 2013).
Carboxymethylcellulose can be the main cause of anaphylactic reaction. Therefore, the low dose of steroids is important to reduce its adverse effects, and maintain its efficacy.

**Future theories:**

1. block the NKGD- activating ligand and NKG2D receptor interaction,
2. halt activated T cells, or
3. modification of the inflammatory cytokine network.

There are new drugs for AA: Anti-CD25, Anti-CTLA-4, Jak 1/2 inhibitor, Anti-NKG2D, Syk inhibitor, Anti-IL-15, Anti-IL-6, Anti-IFNg, Anti-TAP2, Anti-IL-1, Anti-IL-17, and Anti-PDE4. Those drugs acting by blocking the innate/NKG2D response (UBLP3, UBLP6, and MICA), and also by antigen presenting cells/sentinel (HLA, TAP, and IFN-g) targeting adaptive immunity such as IL-15 by driving NKG2D axis, or through blocking Th1 cytokines by the use of Jak inhibitors

**10.2 Therapeutical Options:**

**10.2.1 Steroids:**

**10.2.1.1 Intralvesional Corticosteroids**

The national ambulatory medical care survey (NAMCS) indicated that topical and intralesional triamcinolone were the most commonly prescribed treatments for AA and then betamethasone propionate, followed by minoxidil as a second line therapy (Mukherjee et al. 2009). The most used one for limited scalp AA is triamcinolone acetonide, and remains as the drug of first choice for localized patchy AA, with a good response for most of patients (Ganjoo et al. 2013). It used in a concentration range of 2.5-10 mg/ml. The preferred dose for using against AA is 5 mg/ml with a maximum volume of 3 ml into deep dermis level or just beneath the dermis, with a treatment duration of 4-6 weeks intervals. The pain at the position of injection can be reduced by using mesotherapy multi injectors with 5-7 needles, or by the use of topical anesthetics, preferably before the beginning of the therapy. This mesotherapy is used for severe AA and also for AA in eyebrows, even if the patient suffers from contracts or increased intraocular
pressure (Galan Gutierrez et al. 2009). The parenteral use of corticosteroids into the affected area mainly into its deep dermis and upper subcutis is considered as the best method for the localized AA mainly for adults, where the use of 2.5-5 mg/ml for the eyebrows and face can cause glaucoma, cataract and retinal vascular occlusion. The use of high dose of triamcinolone acetonide 10 mg/ml, as an injection of 0.05-0.1 ml per site spaced 1 centimeter can result in a good response (Wang et al. 2012). The use of systemic drugs for AA can modify the course of disease, while the locally used one will only alter the underlying conditions (Seetharam 2013).

The most side effects of steroids are increased appetite, insomnia, mild edema, transient hyperglycemia, facial flushing, sodium and water retention, and also growth retardation which limits its use for children and also relapses may be seen after stopping its use (Bajaj et al. 2008).

Figure (15): Intrallesional corticosteroid injection with a 30-gauge needle into a patch of AA (Bolduc and Shapiro 2001).

Intrallesional steroids pass the barrier zone and make a subepidermal depot. The injection of triamcinolone is by the use of 0.5 inch long, 30 gauge needle, fitted to an insulin syringe (Gonjoo et al 2013). Most types of AA can be treated with intrallesional triamcinolone acetonide 5mg/ml every 4 weeks for 3 months (Bansal et al. 2013). The first time was in 1985 in which intrallesional steroids had been used. It was hydrocortisone, but nowadays the most used one is triamcinolone. It is injected in concentrations of 2.5 - 10 mg/ml till a maximum dose of 20
mg/ml in the deep dermal/upper subcutaneous place is reached. It is mainly injected at 0.5- to 1-cm intervals every 4-6 weeks, and the therapy is stopped if there is no response after 6 months (Alkhalifa 2011).

The use of high doses of triamcnicolone acetonide (40mg/mL), paramethasone acetate (20mg/mL) or betamethasone (3mg betamethasone sodium phosphate and 3mg betamethasone acetate) as injections is combined with massage after each injection to avoid atrophy. It is important not to make massage in fronto-parietal areas because crystalize deposit formation may lead to thrombosis in central retinal artery.

Ganjoo et al. (2013) considered that the drug of choice for AA is the use of intralesional corticosteroids mainly triamcinolone acetonide for 24 weeks, especially for those with AA less than 50% of the scalp, showing a higher percentage of response compared to other studies. Out of 60 patients 28 responded early, 29 responded in a period of 24 weeks and just 3 patients did not respond to this regime of treatment. This method can show also side effects like transient atrophy in 3% of patients and telangiectasia in 16%.

Most of studies say that if there is no response after 6 months of injection, then the treatment should be stopped. The evaluation of efficacy may range from 12-16 weeks or 24 weeks, and the effect of triamcinolone acetonide can persist for at least 9 months (Gonjoo et al. 2013). The response rate of AA to the steroids is determined mainly by the disease severity and time of intervention, but not by the administration form of steroids (Yang et al 2013). Patients with a longer history of AA of more than 1 or 2 years has less response rate when compared with patients of recent AA (Uchiyama et al 2012).

AA can spontaneously recover, specially the subtype ADTA. When more than 80% of the area of AA return to normal state and are covered with hairs of more than 1 cm length, and there is no hair loss anymore for at least 6 months after remission, complete remission can be seen (Lew et al. 2009, Brzezinska et al. 2014). Although there may be relapse of hair fall with 10% in ADTA and 86% in AA, spontaneous remission occurs in up to 80% of patients with limited patchy hair loss of short duration of less than 1 year (Gonjoo et al 2013).
10.2.1.2. Topical corticosteroids

Topical steroids induce a T cell mediated response; they cause the inhibition of the T lymphocytes activation (Sardesai et al. 2012). Topical application of steroids can be considered as first line treatment of AA just like intralesional corticosteroids (Hordinsky 2013).

Topical corticosteroids can be used in many topical forms like creams, gels, foams, and lotions. Betamethasone valerate is the most widely used with a high efficacy. AT and AU are less responding. Betamethasone valerate foam can be effective for most patients when used twice daily for 12 weeks.

Topical corticosteroids can be used alone or in combination with other drugs or to be mixed with other medicines to make new formulations in order to get the best response. Moderate to potent corticosteroids are used for AA, but 0.25% desoximetasone as cream showed no response. With clobetasol propionate used for 6 day in a week for 6 months the first response was seen after 6 weeks, but only less than 30% of patients responded to the therapy (Tosti et al. 2003, Wasserman et al. 2007). However, the use of 0.05% clobetasol propionate foam with minoxidil and anthraline showed good results for AT and AU in randomized, double-blind, placebo–controlled studies. The most seen side effects of this group are folliculitis, erythema, acne form eruption, atopic striae, telangiectasis and hypertrichosis (Galan Gutierrez et al. 2009).

Another drugs related to this group are fluocinolone scalp gel, halcinonide cream, and dexamethasone in penetration enhancing vehicles (Wasserman et al. 2007).

10.2.1.3. Systemic Corticosteroids

Extensive AA is mostly treated with systemic corticosteroids. Pulsed prednisolone is considered as one of the most used methods in the treatment of AA, where the response rate can be increased by the use of triamcinolone acetonide. AT is far less responsive to this therapy than patchy alopecia areata.
There are some side effects which limit the use of corticosteroids like adrenal suppression, hypertension, hyperglycemia, weight gain, sodium water retention, dysmenorrhea, immunosuppression and acneiform lesions. Atrophy can be avoided or reduced by avoiding the use of too large volumes or too frequent injections, or insufficient depth of injection (Wasserman et al. 2007). The signs of early clinical response can be usefully identified dermoscopically (Ganjoo et al. 2013).

An important and effective type of treatment is the pulse therapy of steroids like \textit{methylprednisolone} as compared with oral prednisolone therapy. It is considered as the first line of therapy in most studies. It can be used in a concentration of 5mg/kg/day methylprednisolone every 2 weeks for 6-12 months, depending on the severity of the disease or it can be used in a concentration of 10mg/kg/day for 3 consecutive days, leading to a good result of hair regrowth of more than 50% in Taiwan (Yang et al. 2013). Sharma (1996) shows a significant growth with oral prednisolone pulse therapy with 300 mg for 3-6 months with a result of 63% hair regrowth in severe AA, although there is poor response in patients with long lasting cases of more than 2 years which started in childhood, AU, AT, ophiasis, atophy and nail involvement. In those cases the weekly pulse therapy with 200 mg prednisolone can be effective in severe AA.

The oral minipulse dose of \textit{betamethasone} for 6 months can also show a good response in 43.7% of patients, but not in those with AT or AU. In case of stopping the drug use relapses can be seen, while another study from Deshpande et al. (2011) shows a maintained response after 1 year of stopping the use of oral steroid in patients with AU and AT. The response can be seen in most patients within the first 3 months of treatment. Scalp irritation and local erythemia was mild and reversible after stopping the therapy (Sharma 1996).

Another method of treatment is the use of 500 mg \textit{methylprednisolone} i.v. for 6 months where it is used each month only for 3 continuous days. It will show a good response in severe AA (Dehghan et al. 2013). Methylprednisolone at high concentrations for 3 days per month shows good results in patients with multifocal AA and AT. In a comparison between the use of 3 regimes for the treatment of AA, the first group was treated with dexamethasone 0.5 mg/day
for 6 months, the 2nd group was treated with triamcinolone acetonide 40 mg once a month for 6 months and the third group with oral prednisolone 80 mg for consecutive days once every 3 months. Oral prednisolone gave a good response, and with less side effects with triamcinolone than dexamethasone (Bajaj et al 2008). The use of oral prednisolone in minipulse regimen of low dose of 30 mg daily at morning for 3 consecutive days every week for 6 months showed accepted response in most patients. The severe forms (AT and AU) showed low response (Bajaj et al 2008).

Prednisolone as a long term therapy or for short term in the form of i.v. methylprednisolone, or in tapered doses given each week for the period of 3-6 months gives a good response in patients with AA. The use of 300 mg prednisolone weekly for 6 months showed a good response in more than 60% of patients (Otberg 2011, Kar et al. 2013). The response for steroids is reduced when the duration of the AA is longer than one year. Methylprednisolone in a dose of 2.5 to 10 mg/kg can be used for those patients who do not respond to other drugs. More than 30% of 85 patients showed a complete hair regrowth when treated with methylprednisolone as injection. This drug should be stopped after 6 months if there is no response. This method is effective for both adults and children (Yang et al. 2013).

Immunosuppressant drugs like cyclosporine, systemic corticosteroids, methotrexate or sulfasalzine, are systemic drugs used for the treatment of AA, although none of the topical, intralesional or systemic therapies of AA are curative (Otberg 2011). The oral use of prednisolone 80 mg once a month for 6 months, or triamcinolone 40 mg once monthly for 6 months are more effective and safe compared to the use of dexamethasone 0.5 mg/day for 6 months (Bajaj et al 2008). Other side effects of corticosteroids are fluid and electrolyte abnormalities, hypertension, hyperglycemia, increased susceptibility to infection, osteoporosis, acute adrenal insufficiency fever, myalgias, arthralgias, and malaise, growth retardation, behavioral disturbances, cataracts, and Cushing syndrome (Wasserman et al 2007). Relapses occurred after stopping the therapy. This is one of the most points that make the patients afraid and may worse their psychological situation (Bajaj et al 2008).
AA can be also treated by **phenolisation and intravenous dexamethasone pulses** (in a dose of 60 mg i.v. in 5% dextrose for 4 months), where phenol is considered as antipruritic. Phenol also coagulates proteins at a concentration over 80%; phenol can be also considered as a bactericide (>1%), a fungicide (>1.3%) and a local anesthetic. It has a burning sensation when it is used on the skin. Phenol applied all over the bald patches of AA, where it prepared in a container of 1 ml in a concentration of 88% and dipping a bud in phenol then applied on the skin, each 15 days as interval, the result seen after 1 months (Chikhalkar 2014). Pulse therapy with high doses of corticosteroids with long intervals show a high benefit to risk ratio (Otberg 2011).

### 10.2.2-Immunotherapy

The mechanism of action of topical immunotherapy is through sensitization of the skin with an allergen leading to a delay of eczematous reaction which leads to hair regrowth by displacing the lymphocyte infiltrate that is associated with AA. Most of the patients show well hair regrowth of 50%-60%. It is less effective for those with severe cases of AA, and it will be better to stop the treatment if there is not any response after 24 weeks (Galan Gutierrez et al. 2008). Side effects are itchy, uncomfortable rash (Lew et al. 2009). Contact sensitizers induced allergic contact dermatitis which can be achieved by the use of 2-ethylhexyl acrylate in wig fixing adhesive tape (Trochia et al. 2008).

Hair regrowth related to alteration of CD4+ /CD8+ cells ratio is due to the immunomodulatory effect. The peribulbar region is shifted to the interfollicular region, and antigenic stimulus elimination decreases the stimulatory effect of T cells. Antigenic competition through inhibiton of the immune response is mediated by T cells and also through reduction of proinflammatory cytokine production (Gutierrez et al. 2009).

#### 10.2.2.1. Diphenylcyclopropenone and squaric acid dibutylester:

Diphenylcyclopropenone (DPCP), squaric acid dibutylester (SADBE) and dinitrochlorobenzene (DNCB) are sensitizers. The first used topical sensitizer was DNCB, however, due to its mutagenic side effect in Ames test it is no longer used. DPCP was first synthesized in 1959. It is
degraded with UV light; therefore the patient should be protected from light for at least 6 to 48 hours (Wasserman et al. 2007). **DPCP is the topical sensitizer of choice.** It is lightsensitive, and for this reason it should be protected from light. **SADBE** is expensive and not stable in acetone. SADBE needs refrigeration and it exerts higher instability in acetone than DPCP (Wasserman et al. 2007). There are some drugs which increase the efficacy of topical immunotherapy like fexofenadine hydrochloride. Hordinsky (2013) suggested that topical immunotherapy can be considered as the first line treatment of AA.

The most observed side effect of SADBE is lymphadenopathy, while the more common side effects for DPCP are scalp eczema and failure of sensitization. In spite of its side effects DPCP is preferred by some physicians for treatment of AA due to its greater stability in acetone and also because of its longer shelf life. Regrowth rate is equal between DPCP and SADBE. When DPCP is applied to half of the scalp first and subsequently applied to both sides. If a unilateral response occurred, 77% of patients mounted an initial unilateral response and 30% hat complete bilateral regrowth (Mukherjee et al. 2009). Other side effects of SADBE are pruritus, mild erythema, scaling, post auricular lymphadenopathy, contact urticarial, post-inflammatory hyper- and hypo-pigmentation, erythema multiforme, facial or eyelid edema, fever, flulike symptoms, anaphylaxis, dyschromia in confetti and vitiligo (Amin et al 2013).

DPCP therapy causes changes from the cytokine milieu to the T cells and also the follicular microcirculation. The response to DPCP therapy may range from 1 to 39 weeks at first response, and the main response is 4 to 24.8 (El Khoury et al. 2013).

One of the important points in the treatment of AA is the follicular delivery. Therefore, the **Non Structured Lipid Carrier** (NLCs) loaded with squaline is used mainly for this purpose where the percutaneous absorption and follicular penetration of diphencyprone delivery increased by the use of squaline containing NLCs. Also NLCs is well controlled and a modern delivery system. It has the ability to penetrate the hair follicles due to fusion with sebum or opening of inactive follicles, when it is used with a greater amount of hydrogenated soybean phospholipid choline (Lin et al. 2012).
The use of topical immunotherapy with DPCP can induce expression of HLA-DR in epidermal keratinocytes in 6 out of 13 cases, where it reduced the abnormal expression of both HLA-ABC and -DR antigens in the epithelium of lower hair follicles in AA (Bröcker et al 1987). Application of potent contact sensitizers to the skin causes immunomodulation of the skin and its appendages. The CD4+/CD8+ ratio in the peribulbar infiltrate of AA lesion is 4:1 (Wasserman et al 2007). Perifollicular lymphocytes apoptosis and changes in the CD4/CD8 lymphocyte ratio, and also interleukin-10 secretion are caused by DPCP. The use of SADBE and and SADBE-induced MDSCs (myeloid-derived suppressor cells) interfered with autoreactive T cell proliferation (Singh et al. 2011).

The hair regrowth of hair follicles can be achieved after 48 hours of the topical use of 2% solution of DPCP in acetone without the exposure to sun light and to be washed after 28 hours. 55.5% of patients respond to this type of therapy, and 33% show relapses. It has been found that the alteration in response rate depends mainly on severity of AA, duration of treatment, age of the patient, and psychological situation of the patient (Akhyani et al. 2009). The main side effects of DPCP are dermatitis and cervical lymphadenopathy; it is also considered as very sensitive to light (Lin et al. 2012). Besides, this group of drugs shows a number of other side effects like urticaria and vitiligo. DPCP showed in a study with 34 patients that 79.4% have a good response and only 29.3% show no response. Those patients were suffering from the following side effects: itching (85.3%) contact dermatitis (58.8%) blistering (17.6%) and cervical lymphadenopathy (17.6%), also hyperpigmentation, hypopigmentation, vitiligo, contact urticaria, and erythema multiforme like reaction were seen in those patients after treatment with DPCP in a concentration of 0.001%, and further increased to 0.01%, 0.1%, 0.5%, 1% and 2% till erythemia and pruritus were observed (El Khoury et al. 2013).

In a study of Bolduc and Shapiro (2001) DPCP 2% was applied to a 4-cm circular area on the scalp to sensitize the patient. Two weeks later, a 0.001% DPCP solution was applied to the same half of the scalp. Then the concentration of DPCP increased weekly till mild dermatitis reaction occurred, so that low grad erythema and mild pruritus was achieved 24-36 hr after applying DPCP, which was left on the scalp for 48 hr before it washed off.
40% of patients with AU show a good response after 6 months of treatment with DPCP and SADBE. The development of allergic contact dermatitis can be achieved by the use of contact sensitizers which leads to hair regrowth due to local inflammation. This can be achieved by the use of adhesive tapes of 2-ethylhexyl acrylate in a wig fixing adhesive tape (Trochia et al. 2008).

10.2.2.2. Methotrexate:

Methotrexate (4-amino-N-methylpteroylglutamic, MTX) is an immune-suppressant agent of the folic acid antagonist class. It can be used in a dose of 20 mg/week which can result in more than 50% regrowth.

AA can be treated by MTX alone or in a combination therapy with low dose of corticosteroids, oral cyclosporine, isoprinosine, thymentin, nitrogen mustard, dapsone or sulfasalazine (Farhsi et al. 2008). In combination with corticosteroids it can be used with intralesional or systemic corticosteroids to get better results (Hammerschmidt et al. 2014). MTX has a lot of side effects like nausea, diarrhoea, epigastric pain, myelosuppression, mild to moderate leukopenia, megaloblastic anemia and thrombocytopenia. Its side effects include also a transient elevation of hepatic enzymes. The plasma level increased in those taking alcohol. Therefore, folic acid should be used in a dose of 5 mg once a day. Gastric and haematologic side effects of MTX can
be treated with 5 mg folic acid 3 times a week. Another combination therapy of oral prednisolone 10mg/dose and 20 mg/kg with MTX, 20 or 25 mg, results in a complete hair regrowth in 64% by using MTX alone, and in 68% patients treated with combined therapy (Joly 2006). It has been used as antineoplastic agent since 1953, for psoriasis since 1971. In other reports the use as immunosuppressant in the treatment of AA shows in 57% patients a response to this drug (Seetharam 2013).

**Figure (17):** Diffuse AA, top view. Left, before; right, after a cumulative dose of 930 mg methotrexate in combination with corticosteroid during the first 4 months of therapy (60% regrowth).

**Figure (18):** AA totalis. Left, before; right, after a cumulative dose of 320 mg methotrexate in combination with corticosteroids (90% regrowth).

**Figure (19):** Multifocal AA. Left, before treatment; right, after a cumulative dose of 180 mg methotrexate in combination with corticosteroids (80% regrowth).

10.2.2.3. Cyclosporine:

The source is the Norwegian fungus *Tolypocladium inflatum*. It acts by inhibition of helper T cell activation and suppresses interferon gamma production. Cyclosporine is used for those patients with a newly transplanted organ who develop AA (Otberg 2011). Its efficacy increased from
25% when combined with low dose oral prednisolone to more than 88% when used with weekly pulsed methylprednisolone (Wang et al. 2012).

There is a number of side effects which limit its use such as nephrotoxicity, immune suppression, hypertension, hypertrichosis with oral cyclosporine, but not with topical cyclosporine. It acts by decreasing the perifollicular lymphocytic infiltrates through inhibition of primary helper T cell activation. Hair regrowth can be seen in patients with AA after 3 months of treatment with cyclosporine in a dose of 6 mg/kg/day. Also a combination therapy of cyclosporine 4mg/kg/day with oral dose of prednisolone of 5mg/day shows a good response in 25% patients, but the recurrence rate increases after stopping therapy. In another combination cyclosporine is applied with oral methylprednisolone 200 mg 2 times daily. But hypertrichosis limits its use especially for children (Seetharam 2013). 33% of patients show more than 70% hair regrowth if the patient of AT and AU are treated with a monthly dose of i.v. methylprednisolone 500 mg for 3 days with 2.5mg /kg/day for 5-8 months. The use of cyclosporine can be effective against AA also in animal model Dundee bald (Otberg 2011). Cyclosporine A is used in the treatment of AA in its severe cases in adult patients more than for children (Mukherjee et al 2009).

10.2.2.4. Azathioprine:

Azathioprine is a thiopurine analog immunosuppressive drug. It inhibits DNA synthesis causing a decrease in proliferation of cells (T and B lymphocyte). Azathioprine is a purine antagonist, its metabolite 6–thioguanine prevents the function of endogen purines. The disruption of nucleic acid is one of its cytotoxic and immunosuppressive activities. It is a well tolerated drug and gives a good result in treatment of AA. It can be considered also as a cheap medicine. In a dose of 2mg/kg body weight for 4 months (Farhsi et al 2008), the main side effect is myelosuppression which limits its use. It also inhibits the synthesis of Langerhans cells and other antigen presenting cells in the skin. It impairs T cells function and essential components of T cell activation. It is more selective for T lymphocytes than for B lymphocytes. It is used in a dose of 2mg/kg/day for 6 months and shows hair regrow in 52.3% of 20 patients. Its side effects are GIT distress, liver enzymes, mild leucopenia. Also hair regrowth can be seen in patients with
Crohn’s Disease with AT (Goddard et al. 1989). AT can be treated with azathioprine when used for 6 months where the same result can be seen in male and female. It can be used alone or in combination with oral steroids like methylprednisolone. Its main disadvantage is delay of onset of action of 6-8 weeks. The response can be seen after 3 months (Farshi et al. 2010). The patients show a better response with low severity and short duration of the disease.

10.2.2.5. Tacrolimus:

Topical tacrolimus can be used for AA in a dose of 0.1%, due to the immune suppressive effect (Mukherjee et al 2009). Corticosteroids, cyclosporine and tacrolimus act by inhibition of the production of IL 2, while sirolimus acts by blocking IL2R signaling causing the inhibition of the T cells action (Lew et al. 2009). Topical Calcineurin inhibitors like tacrolimus and pimecrolimus inhibit transcription following T cells activation of several cytokines involving interleukin-2, interferon and tumor necrosis factor (Amin et al. 2013). Those drugs are of weak activity or they are not effective against AA (Seetharam et al. 2013) as compared with intralesional or topical corticosteroids (Wang et al. 2012).

10.2.2.6. Biologics:

Biologics are modern immunosuppressant drugs (Seetharam 2013). The main used drugs belong to this group such as adalimumab, infliximab, and etanercept. There was a thought that entanercept is not effective in treating moderate to severe AA (Price et al. 2008). In a placebo controlled study it is shown that efalizumab, as anti-CD11a antibody, is not effective against AA (Tobin 2014). Efalizumab is not effective in the treatment of AA according to a study of Price et al. (2008), where only 8% of 62 patients show response when it is used for AA. It is considered that biological agents involving adalimumab, alefacept (a fusion protein that binds to CD2 and inhibits T cell activation), etanercept (a tumor necrosis factor-alpha inhibitor), and infliximab (a recombinant humanized monoclonal antibody against CD11a) are ineffective against AA according to randomized placebo-controlled studies and individual case reports (Hordinsky 2013).
The use of efalizumab is also effective against AU with other diseases like atopic dermatitis and Hashimotos thyroiditis by inhibiting the T cell activation CD11 in a dose of 0.7mg/kg/Wk for 1 month, then increased to 1.0 mg/kg/wk, showing after 9 months 90% of hair regrowth also in pubic and axillary (Kaelin et al. 2006, Wasserman et al. 2007).

10.2.2.7. Leflunomide:

Leflunomide is another drug which can be used for the treatment of AA, resulting in complete hair regrowth when used for 3 months in combination with adalimumab as shown in a case study (Lazzarini et al. 2014).

10.2.3-Topical Solution of Minoxidil

Minoxidil is one of the most used drugs for AA in form of solution, shampoo, or foams. Some studies consider that minoxidil in a dose of 5% is the more effective than 1% minoxidil, where it shows a rapid hair regrowth compared with low dose. A higher concentration of minoxidil is more effective than low dose (Maitland et al. 1984). The use of 3% minoxidil gives accepted results, where 16 out of 31 patients show good response of hair regrowth; 3 of them show 75-100% hair regrowth (Ranchoff et al. 1989). The use of 5% minoxidil is more effective than 3% minoxidil for the treatment of AT or AU after 1 year of treatment (Epstein 2001).

It can be also used for AT and AU with a beneficial effect. The main side effects of minoxidil are contact dermatitis and facial hypertrichosis.

Its mechanism of action in promoting hair growth is not completely understood, and it needs further investigation. It may cause vasodilatation, angiogenesis, enhanced cell proliferation, and potassium channel opening has been proposed. Minoxidil 5% solution twice daily is used as adjuvant treatment to conventional AA therapy. The use of 1% minoxidil in comparison to the use of placebo shows in 16 out of 26 patients a good result, and 21 in general show a response (Fenton et al. 1983). Another study considered that the use of 3% minoxidil is more effective than the use of 1% minoxidil especially in those with AT and AA (King et al. 1983).
The plan of therapy starts with the history of patient, which is taken by the physician, then physical examination of the hair and nails. Prognosis of AA is important to be known, and also the ratio between the benefit and risk of treatment.

For patients with AA more than 50% of the scalp, DPCP or triamcinolone acetonide injections can be used. If the response is not good or absent after 6 months of treatment, then for 6 months 5% minoxidil solution, topical clobetasol propionate, or short contact anthralin can be used. Minoxidil 5% with intralesional injections of triamcinolone acetonide can be used for the eyebrows (Norris 2003).

Minoxidil acts through opening the potassium channels, increasing blood flow to the hair follicles, and increasing the duration of the anagen growth. Minoxidil alters the matrix cell proliferation at the base of the bulb, which is increased by the uptake of labeled amino acids, production of the hairspecific proteins, and expression of a gene for a hair specific ultra-high sulfur keratin protein, and prostaglandin stimulation in the dermal papillae (Wasserman et al. 2007). The main side effects are irritant dermatitis and allergic contact dermatitis (Mukherjee et al. 2009, Sardesai et al. 2012). Hypertrichosis can limit its use for children as non acceptable side effect. Minoxidil is considered as a well effective drug against AT and AU showing an accepted response represented by the regrowth of hairs o the scalp (Herskovitz et al. 2013). Minoxidil can replace other treatments for AA and can be used as the first line therapy (Hindson et al. 1984). Minoxidil causes hair regrowth by the use of lotion 0.5 mg ointment and 0.5 ml of lotion twice daily. Minoxidil is safe, non toxic, and easy to use; topically applied it causes no changes in pulse rate or blood pressure (Fenton et al. 1983).

In old studies minoxidil was used by crushing minoxidil tablets, which was then diluted to a concentration of 1%. This was used like a cream twice daily for 4-6 months. This showed no response in those patients with AT. Crushing of minoxidil tablets and dilution with proplene glycol 10%, distilled water 20% and alcohol to 100% to make a 3% minoxidil lotion, and applied twice daily for 4 months also showed no effect in patients with AT, but in 2 out of 4 patients with AA it showed hair regrowth (King et al. 1983).
In comparison with other drugs minoxidil is considered as a safe drug and useful with few side effects like dermatitits and headache. Its onset of action is slower than with sulfasalazine. PUVA causes a number of side effects such as dry skin, pruritus, ophthalmic disorders, and is more expensive than minoxidil (Dehghan et al. 2013).

10.2.4-Other Dermatological Treatments

10.2.4.1. Anthralin:

It is one of the oldest drugs used for AA. As an immunomodulator it acts by inhibiting a Langerhans cell mediated immune response, where it induces inflammatory irritant dermatitis when applied at the area of AA to maintain a mild eczematous reaction (Mukherjee et al. 2009). It is used in a high concentration of 0.5%-1% for 15-20 min; and this can be increased to 5 min weekly till 1 hr until low-grade erythema develops, and then continued for 3 months. The patient should be protected from light; the use of 0.1 % is of no therapeutic benefit (Wasserman et al 2007). Its effectivity is through its mild irritation activity, where severe irritation is considered as the main side effect. It has also another important side effect which is staining of the cloths. Anthralin induces irritation through induction of extracellular generation of oxygen free radicals. The reactive oxidant is a potent proliferative and immunosuppressive agent. It inhibits chemotaxis, interleukin 2 production, and cytotoxic activity of natural killer cells. Anthralin is an immunomodulator by inhibiting a Langerhans cell mediated immune response (Bolduc and Shapiro 2001). Anthraline can give a negative result, where erythema can be seen after the use of anthralin. Therefore, a short contact therapy can be used (Sardesai et al. 2012).

10.2.4.2. Dithranol:

Dithranol can induce hair regrowth by its use in a concentration of 0.25%-1% overnight. Dithranol interacts with interferon, tumor necrosis factor and interleukin-10. It can be applied for 30 min and increased gradually till it will be 1 hour of exposure which is a short contact
therapy. Warm water is used to remove the drug from skin to prevent the change of follicular orifices color to dark brown color (Galan Gutierrez et al. 2009).

10.2.4.3. Prostaglandin analogs:

Lanatoprost is a prostaglandin F2-\(\alpha\) analog. Eye drops for patients with AU can be useful, or 0.03% bimatoprost eye drops in a separated day for 1 year can be useful to get a complete regrowth of eyelashes. The solution of lanatoprost is applied by the use of a cotton-wrapped applicator applied once daily and controlled every 4 weeks for 4 visits to the upper and lower margins of one eye (Roseborough et al. 2009).

10.2.4.4. Topical Retinoids:

There are very limited studies for using topical retinoids in the treatment of AA in adults and there are none in children. A study showed that use of retinoid for 3 months in 80 patients caused a 70% response rate with topical steroids, 55% with topical tretinoin and 20% in control. Topical bexarotene, a retinoid X receptor agonist, was studied in 42 patients and showed some efficacy (Wang et al. 2012). A 1% gel of bexarotene is mainly used; its main side effect is mild irritation. Topical tretinoin 0.05%, topical betamethasone dipropionate lotion, and dithranol paste 0.25%, give a good response. However, it needs larger, double-blind, placebo-controlled trials to prove its efficacy.

10.2.4.5. Garlic and Onion:

Garlic and onion, both belong to the Asparagus group of plants. Its effects are induced by diallyl disulfide. The mechanism of action in the treatment of AA is unknown. The combination of topical garlic gel (5%) with betamethasone valerate (0.1% in isopropyl alcohol) which is used in the form of cream two times daily for 3 months and to be placed for 1 hour on the patches of AA each time, can be effective in the treatment of AA. In 19 out of 20 patients a good response for this type of combination therapy was seen, but not for eyelashes or eyebrows. The main active component of garlic gloves is alliin, which is an oxygenated sulfur amino acid, and which will be changed to allicin when the garlic is crushed. This allicin is responsible for the
therapeutic effect of garlic in AA. Hair regrowth begins in the first months of treatment, and after 3 months the regrowth of terminal hairs all over the patches of AA is shown (Hajheydari et al. 2007).

10.2.4.6. Phenol:

Phenol is an aromatic hydrocarbon produced from coal or manufactured from monochlorobenzene. Phenol is considered as antiseptic agent; therefore it can be also used for its antipruritic properties (Kar et al. 2013). It is cheap and can be used easily (Chikhalkar et al. 2013). It is one of the most used drugs against AA for many years. Phenol can penetrate the skin rapidly, which may cause protein keratin coagulation reducing therefore the penetration of other chemical. Therefore, the diluted form of phenol to 50% is considered to be of higher penetration capability (Kar et al. 2013). Chikhalkar et al. (2013) show that 88% phenol at 3 weeks interval is the treatment of joice for stable AA, where it is efficacious with all patients resulting in hair regrowth after 9 weeks of treatment with phenol, represented by the regrowth of pigmented hairs. A study on 50 patients with 88% phenol at 3 weeks intervals in hospital shows that all patients had a good response.

The patients with other than scalpy AA, diffuse AA, or those suffering from other diseases at the same time with AA like cardiac, renal or hepatic problem, also pregnant and lactating women should not be treated with phenol. It has a number of side effects like erythmia and hypopigmentation due to impairment of melanin synthesis (Amin et al. 2013).

Phenol (20%) can be also used in a combination therapy with oral mini pulse betamethsone or 2% minoxidil. This can be more effective and gives a good result compared with the use of phenol alone (Chikhalkar 2014). 1 ml of phenol in a concentration of 88% is applied to the scalp by dipping a bud in phenol. This method is used 5 times in 15 days. Dexamethasone pulse therapy is used for 4 months in a dose of 60 mg i.v. with 5% dextrose. Response represented by hair regrowth can be seen after the 2nd sitting. Phenol can be used also in a combination with oral mini pulse betamethsone or 2% minoxidil. This is more effective than the use of phenol alone (Kar et al. 2013).
10.2.4.7. **Zinc:**

Oral zinc sulphate can be effective for the treatment of AA. Zinc has a potent immunomodulatory effect. By induction of metallothionenin it is an antioxidant. Zinc is also a potent inhibitor of endonucleases, which gives the keratinocytes their crucial role in the catagen phase. This inhibits hair follicle regression. Zinc inhibits tyrosinase enzymes of hair follicle meanogenesis. In general zinc can give good results when used for 6 months. There are no relapses 3 months after stopping the use of oral zinc sulphate (Sharquie 2014).

10.2.4.8. **Botulinum Toxin Type A:**

It contains a protein complex purified from the bacterium *Clostridium botulimum*. It had been used for long time for neurological conditions by blocking the transmission of overactive nerve impulses locally, due to inhibition of muscle contraction by preventing the release of ACh neurotransmitter at the neuromuscular junction. It is used for the treatment of AA according to the severity of the disease (Cho et al. 2010).

10.2.4.9. **Calcipotriol:**

AA treatment can be achieved by the use of Vitamin D, where Th1 cell proliferation and cytokine production are inhibited by the addition of 1,25(OH)₂D₃ to CD4 T-cells, targeting immune cells like monocytes, macrophages, dendritic cells, as well as T lymphocytes and B lymphocytes. This causes the reduction in the creation of IL-2 and interferon-Y by CD4 T-cells, and it also increases the production of IL-5 and IL-10 (Kim et al. 2012). 1,25(OH)₂D₃ induces stimulatory activation through the inhibition of the differentiation of monocytes into dendritic cells and impedes T cells. 1,25(OH)₂D₃ binds to vitamin D receptors which interfere with nuclear factor kappa B leading to the transcription of IL-12. Therefore, vitamin D causes changes in the immune function (Kim et al. 2012).

AA can be related to vitamin D deficiency, vitamin D resistant rickets, or vitamin D receptor mutation. Vitamin D level is low in AA patients (< 30 ng/ml) (Mahamid et al. 2014). AA can be treated with topical calcipotriol, where Vitamin D is important not only for the bone metabolism and calcium regulation, but also for cutaneous immune modulation, where it acts
through the regulation of epidermal cell proliferation and differentiation and modulation of cytokine production.

10.2.4.10. **Glycyrrhizin and glycosides of paeony:**

Total glucosides of paeony capsule and glycyrrhizin are used for mild and moderate AA. Glycyrrhiza is used in a dose of 600mg orally 3 times a day, with 10 mg Vitamin B2 for 3 months. Glycyrrhiza can act by inhibiting the ratios of CD3+/CD4+, and CD3+/CD8+ and also Th/Ts. Total glycosides of paeony capsule inhibit T lymphocytes generation, and prevent the damage of hair follicles. It is used in a dose of 600mg orally 3 times a day, with 10 mg Vitamin B2 for 3 months. Patients should be always in contact with their doctors to observe the side effects and the response to the treatment (Yang et al 2012).

10.2.5- **Sulfasalazine:**

Sulfasalazine is a systemic drug and a derivative of mesalazine (5-aminosalicylic acid). It is a 5-lipoxygenase inhibitor which inhibits the release of prostaglandin E2 and interleukin-2. It acts as an immune-modulatory and anti-inflammatory drug, and inhibits inflammatory cell chemotaxis and cytokine and antibody production, T cell proliferation, natural killer cell activity, and antibody production. Sulfasalazine also inhibits the T cell cytokines interleukin IL-2, -6, -1, and -12, interferon gamma, and the monocyte/macrophage cytokines IL-1, and TNF-α (Amin et al. 2013).

It is a systemic treatment of AA, where 23% of patients have noticed cosmetically acceptable regrowth of their hair (Ellis et al 2007). Sulfasalazine can be used in a dose of 0.5 g twice daily for 1 month; then the dose is increased to 1 g twice daily for 1 month and finally to 1.5 g twice daily for at least 3 months, showing that 23% of the patients will respond to the therapy. When the drug is applied twice daily for 4 months, complete hair regrowth occurred in 45.5% of patients (Ellis et al. 2007), with a rate of recurrence of 25%. Similar results were obtained by Otberg (2011). In this study sulfasalazine was used in a dose of 1500 mg 2 twice daily for 6 months where 25.6% of 39 patients showed a complete hair regrowth and 30.7% a mild to
moderate regrowth. Complete blood counts and liver function tests have to be performed at first months of therapy (Otberg 2011).

Its side effects are not severe (Rashidi et al 2008). These are gastrointestinal distress which can be avoided by the use of enteric coated tablets of sulfasalazine, or to be taken with foods, and other side effects like dizziness, headache, fever, rash, hematological abnormalities, and hepatotoxicity (Seetharam 2013).

10.2.6- H1 Antihistamines:

H1-Antihistamines is a group of drugs that can be also used for the treatment of AA, such as fexofenadine, which acts by increasing the efficacy of contact immune therapy in atopic background of AA patients. Some antihistamines can inhibit or reduce the keratinocyte production of chemokines, as an example the type CXCL 10, and through this mechanism it can support the treatment of AA (Ito et al. 2013).

Oloptadine can act by the reduction or modulation of T cell chemotaxis toward CXCL 10, reducing CXCR3 expression, which is increased in AA patients, and F-actin polymerization and calcium influx. CXCR3 can promote Th1/Tc1 cells. Oloptadine can then reduce CD4+ and CD8+ T cells chemotactic activity (Ito et al. 2013).

10.2.7- Iron Substitution:

Iron deficiency associated with AA was treated orally (tablets, elixir, capsules, etc), with carbonyl iron, polysaccharide-iron complex or by blood transfusion in severe cases. Ferrous sulfate can be used in a dose of 300 mg 3 times a day as the cheapest and most effective drug. It can be used with ascorbic acid in order to increase its effectiveness. It may cause some side effects, mainly GIT disturbances. Iron in the form of i.m. or i.v. injection as iron dextran is used for those who cannot take oral doses of iron, although it can cause local pain or muscle necrosis at the site of injection, with fever, urticarial or sometimes rheumatoid arthritis. Blood test is
important to check the hemoglobin concentration every 3-4 weeks, which should not exceed 2g/dl (Trost et al. 2006).

10.2.8- Prostaglandine Analogues:

Bimatoprost and Lanatoprost are used in the treatment of AA. There is an association between prostaglandine receptors in dermal papilla and outer sheath of the hair follicles with their regrowth. These compounds can be used for patients with eyelashes and eyebrows hair loss, for 6 weeks, once a day. Those patients show a good response with no serious side effects. Sometimes mild eye irritation or hyperemia is seen (Vila et al. 2010, Zaheri et al. 2010).

10.2.9- Photochemotherapy:

UVA exposure can be used for the treatment of AA. The patient’s scalp is exposed to ultraviolet radiation.

- **PUVA-turban** is a method of administering a dilute psoralen solution (8-methoxypsoralen 0.0001%) selectively to the scalp for 20 minutes using a cotton towel as a turban.
- **Excimer laser**: treatment of alopecia areata patches with the 308 nm excimer laser; the use of excimer laser in children with AA has been reported to have a good success rate.
- **Fractional photothermolysis laser**: a lot of controlled trials are needed to improve its efficacy.

10.2.9.1. Psoralen plus ultraviolet A (PUVA):

The use of PUVA is safe for treatment of AA, but its side effect of relapses may limit its use, while the use of narrow band ultraviolet B (NB-UVB) phototherapy is of high efficacy and tolerability in the treatment of many inflammatory and neoplastic skin diseases (Alkhalifa et al. 2010). There are many factors that affect the response to this type of therapy; those factors are
nail changes, a personal history of atopy, duration of AA, extent of AA, and age at the onset of the disease. The main factor which plays an important role in the treatment of AA is the severity of the disease (El Khoury et al. 2013). A study by Bayramgürler et al. (2011) shows that the use of narrow band ultra violet (NB-UVB) treatment for 3 times a week with 0.2 J/cm², not more than 30 weeks gives a good response and hair regrowth. But it should be stopped if there is no response to this therapy.

Another study from Kamel et al. (2011) shows that the use of phototoxic psoralen and ultraviolet A therapy is similarly effective for AA as the use of 0.1% 8-methoxy psoralen (8-MOP). In 35 patients, placed under this therapy of topical 8-MOP and followed by UVA irradiation in a dose of 22 ± 8.3J/cm², 57% of them were with a positive result, and 40% showed a complete hair regrowth. The combination of UVA in a cumulative dose of 7.5-39.6 J/cm² with topical 8-MOP can be effective against AA and results in a good response (Acikgoz et al. 2013). The use of UVA in cumulative doses from 7.5 to 39.6J/cm² 3 times a week with 15-24 sessions after 8-MOP application is one of the modern and rising models of treatment of AA. Most patients show a cosmetically accepted regrowth of hairs (Acikgoz et al. 2013).

PUVA with cyclosporine 200 mg for adults or 100 mg for children for 16 weeks, showed more than 50% hair regrowth. After that the dose should reduced, because squamous cell carcinoma can develop (Park et al. 2013).

PUVA can be more effective for AT and AU when combined with oral steroids. Its side effects are dangerous and should be taken in attention like mild erythema, burning and increased risk for melanoma. When the NB-UVB phototherapy is ineffective in AA, it can show a response in some patients when it is used in combination with i.m. triamcinolone acetonide 40 mg/ml (Bayramgürler et al. 2011). UVB treatment can be achieved by its use for 3 times a week with 0.2J-0.3/cm² for skin and this dose can be increased up to 1.8J/cm², till a response occurs. Then it will be used for twice a week, and when the hair regrows, again it is reduced to once a week. This method should be stopped when there is no response after 10-12 months or 30 sessions (Bayramgürler et al. 2011).
Treatment of AT with Turban PUVASOL: AT can be treated with the exposure to sunlight with the use of 8-MOP 1%, using a clean piece of absorbent cotton cloth in a solution for 30 seconds and wrapped for 5 min 4 times. This can be used for a longer time of 5 min for 3 times a week around the scalp at the morning in shadow to avoid the exposure to sunlight. This method can result in a complete hair regrowth after 4-6 months as shown in a case study of a 41 years old female with AT who did not respond to a treatment with minoxidil and betamethasone. A similar result was shown for a child of 8 years (Sornakumar et al. 2010).

Sharma et al. (1990) had considered a good response of the daily local use of 8-MOP (0.75%) for 3 months. Within this period after 30 min of drug application the skin was exposed to sun for half a minute. This exposure time was increased by 15 seconds after 2 weeks till 2 min were reached as maximum time of exposure. 71% of 20 patients showed complete hair regrowth, and this method of treatment is effective in those patients with ophiasis and atopy (Galan Gutierrez et al. 2009).

The main side effects are erythema and pruritus. A regrowth rate of 35-38% can be achieved by the use of topical or oral PUVA (Mukherjee et al. 2009).

10.2.9.2. Excimer laser:

A 308 nm monochromatic excimer lamp can be used for the treatment of AA. With this method 14 of 16 patients showed a cosmetically accepted hair regrowth by the use of a dose of 150-200 MJ/cm², for 1-2 weeks of UV. It is considered as a cheap method as compared with laser (Ohtsuki et al. 2013).

Diode laser acts by reduction of perifollicular lymphocytic infiltration through scattering of perifollicular lymphocytes. As a result laser increases the anagen stage and prevents the telogen phase. Fractional laser causes the induction of minor trauma and wound healing process facilitates the hair regrowth. Zakaria et al. (2004) showed that a 308 nm excimer (Tatlos-Wavelight laser Technology AG, Erlangen, Germany) with 50MJ/cm², 2 times a week for not more than 24 sessions and increase in dose after 3 months, was effective in AA partialis, but
was not effective in AT and AU. Its side effects are erythemia (not severe), and hyperpigmentation. 308-excimer laser can give acceptable results in 41.5% patches of AA. However, this type of treatment can show a poor result with AT and AU (Seetharam 2013).

10.2.9.3. Treatment of AA with functional photothermolysis laser:

Laser of different wavelengths can be used and give a good result. It acts by induction of T cell apoptosis causing hair regrowth. It causes thermal damage pattern named microthermal treatment zones, maintains the stratum corneum intact and gives fractional microscopic thermal columns to the dermis. One of the types of lasers used is Mosaic lutonic Inc, Gyeonggi Korea. It is used for a period of 24 weeks with a pulse energy of 10-15 MJ and density of 300 MTZ/cm²/pass. The response occurred after 1 month and complete regrowth of hairs occurred after 6 months of therapy (Yoo et al. 2010).

10.2.10- Psychological Support:

It plays an important role in the treatment of AA to educate patients about their situation and the benefit of treatment and its urgency, and also encouraging the patients which is so useful for reducing the severity of AA.

Patients suffering from AA, AT or AU mostly have anxiety and depression. Those patients can be treated hypnotically or psychologically in order to get a wellbeing healthiness. Hair regrowth can be seen after 3-8 sessions of hypnotherapy in patients who failed to respond to other types of therapy (Willemsen et al. 2010).

10.2.11- Different other Methods:

There are many techniques to deal with AA for those who do not accept the use of drugs. One of those techniques is the use of hair pieces (wigs, demi wigs, toupees, cascades and wiglets). It
is an expensive procedure where it needs a regular shampoo for long time while these hair pieces last just few days. Another way is the use of synthetic hair fibers, which last longer than hair pieces and are also of low cost, but it needs bonding, gluing or sewing but no shampoo. Another way is the use of Tattoo for AA in eyelashes and eyebrows. Traction alopecia and hair breakage from glue and clips is considered as its disadvantage (Seetharam et al 2013).

There are other drugs used for the treatment of AA which are traditionally used like Chinese herbal medicine, carpronium chloride hydrate, liquid nitrogen cryotherapy, cepharanthine, and mono-ammonium glycyrrhizinate. All these therapies need double-blind, placebo-controlled trials to be accepted, like topical azelaic acid, topical tretinoin 0.05%, topical onion juice, and intralesional candida antigen injections (Seetharam et al. 2013).

Mesotherapy needs randomized controlled studies in order to evaluate its efficacy. It employs multiple injections of pharmaceutical and homeopathic medications, like plant extracts, vitamins, and other ingredients into the target tissue (Amin et al. 2013).

The use of the acupuncture method is better than the use of other oral drugs for the treatment of AA. Acupuncture and pricking of plum-bossom needle therapy can be compared to oral drugs in a study on two groups of patients. One group of 43 cases treated with the puncture method and the second group included 35 cases treated with oral administration of cystine tablets, vitamin B1 and topical wash minoxidil lotion (cystine tablets 0.1 g, orally, 3 times a day; Vitamin B1 20 mg, 3 times a day; 2% minoxidil solution for topical application, twice a day). The result was 58.1% and 97.7% in the treatment group and 34.3% and 77.1% in the control group, respectively. The statistical differences in the curative rate and total effective rate between the two group was p<0.05 (Qiyu et al. 2011).

**10.2.12 Combination Therapy in the Treatment of Extensive AA:**

There are a lot of combination therapies used for the treatment of AA with topical and systemic drugs involving steroids, minoxidil, anthralin, azathioprin, sulfasalazine, cyclosporine, methotrexate, and biologicals (Deshpande et al. 2011).

80% of patients show a good response (Deshpande et al. 2011).
A study from Park et al. (2013) shows that the combination therapy of oral cyclosporine in daily dose of 200 mg for adults and 100 mg for children for 16 weeks, combined with methoxsalen topically 20 min before exposure to UVA which is applied twice a week for 16 weeks caused a response in 18 of 41 patients with severe AA. The main side effects were generalized edema, hypertension, abnormal liver function test, abnormal lipid levels, and hypertrichosis. Another side effect of PUVA is cutaneous squamous cell carcinomas of the skin. Therefore, attention should be taken in those patients with a history of malignancy (Park et al. 2013).

**Treatment plan according to extent of AA:**

- **less than 25%:**
  - 0.05% clobetasol propionate and/or 0.05% retinoic acid and/or 2%-5% minoxidil
  - Wait and control
  - Intraleisonal corticosteroids
- **between 25 and 50%:**
  - Under control
  - Intraleisonal corticosteroids
  - Use of a triple therapy: Intraleisonal triamcinolone acetoinide +5% minoxidil (twice a day) + topical clobetasol propionate (30 min after minoxidil)
  - Combined therapy (5% minoxidil twice a day + 1% anthralin cream 1 hour a day)
- **more than 50%:**
  - DPCP (2 applications a week for 24 weeks)
- **no response** after 24 weeks:
  - 5%minoxidil–1% anthralin cream plus potent topical steroid.

Treatment of mild AA is easier than severe AA, and the risk of relapses increased with the duration of disease. Therefore, the topical steroids show a lower improvement rate after 24 months (Uchiyama et al. 2012).
10.3 Alopecia Areata in Children

AA is one of the most common diseases in children. It can be seen in those till age of 20 (Wang et al 2012). AA can be seen also in monozygotic twins and can be related to the family; many of the cases can spontaneously remove without any need for treatment (Seetharam 2013). This remission could be more than 80% in those patients with a history of less than 1 year where good education and psychological support could be of benefit (Brzezinska-Wcislo et al. 2014).

AA may be associated with other diseases. One of the most important diseases is dental disease like caries, chemical or mechanical damage, tooth bridge, etc., so that the remission of the dental problems will show reduction of the hair loss in children. The main cause of AA in those patients is the presence of immune mediators in both AA and dental infection. Where inflammatory reaction in the dental root canals occurred due to the dental infection, this will cause pulp tissue necrosis leading to the movement of germs to the periradicular zone causing infection due to bacterial irritation (Victor Samuel et al. 2012).

AA is mainly seen in children who are in the primary school. It is important to cheek the thyroid hormones in children having long standing AA. It occurs also in siblings and it is affected by environmental factors (Menon et al. 2012). In a study of Reeve et al. (1996) 7 out of 12 children show anxiety disorders including simple phobia, also with criteria of dysthymia.

Children can suffer from other dermatological diseases which are similar in symptoms to AA like Trichotillomania and Tinea capitis (Ganjoo et al. 2013). AA can be differentiated from Tinea capitis and Trichotillomania, because the presence of inflammation or at least mild scaling is the main characteristic feature of Tinea capitis, while Trichotillomania is characterized by irregular or bizarrely shaped and rough lesions. It is also difficult to differentiate diagnostically AA from telogen effluvium. It will be better to use scalp biopsy instead of hair pull test, where AA shows the presence of dystrophic anagen hair, while telogen effluvium shows the presence of pure telogen hair. AA can be also related to Down syndrome in children where the frequency of AA is increased with 8% in children with Down syndrome (Madani et al. 2000).
Treatment of AA in children is considered as a big subject of analysis and work till now. It depends on the psychological condition of the patient, acceptance of the treatment, parenteral anxiety, frustration, and the family situation of the patients (Wang et al. 2012), so that the therapy of AA is limited in children due to less tolerability and the potential side effects (Thappa et al. 2013). Treatment of AA is so important especially in children and therefore should be done with care even if the period of treatment takes long time (Menon et al. 2012).

10.3.1 Treatments used for AA in Children:

Corticosteroids, minoxidil, topical and systemic immune suppressants and immune sensitizers, topical corticosteroids are commonly used in children, because they are painless and have relatively benign side effects (Mukherjee et al. 2009).

- **less than 10 years old:**
  - Minoxidil 5% solution
  - Topical corticosteroid or short-contact anthralin

- **more than 10 years old, with less than 50% of scalp involvement:**
  - Intralesional corticosteroids every month
  - Minoxidil 5% solution
  - Topical corticosteroid or short-contact anthralin

- **more than 10 years old, but more than 50% scalp involvement:**
  - Topical immunotherapy with diphenylcyclopropenone, squaric acid dibutylester and dinitrochlorobenzene
    - If good response, continue immunotherapy as needed
    - If poor response, consider minoxidil 5% solution and topical corticosteroids
    - Psychological treatment is important to increase the possibility of healing

- **Minoxidil:** AA in children can be treated by the use of many drugs; one of those drugs is minoxidil, although minoxidil may show cardiovascular side effects by the treatment with 2% minoxidil especially for AT and AU. Most of those children treated with minoxidil can
show a good response and hair regrowth after 6 months of treatment. Minoxidil in different concentrations (1%-3%-5%) can produce good results in children with AA, although it may be expensive for the patients (Wang et al. 2012). Topical minoxidil is restricted in some patients where it may cause hypertrichosis, which is represented by growth of long pigmented hairs on the face, trunk, and limbs and on the neck; also hypotension, tachycardia and dermatitis can be seen (Herskovits et al. 2013). Minoxidil is used with corticosteroids due to the immunomodulatory effects of minoxidil on the hair follicles autoimmune attack (Wang et al. 2012).

- **Topical immunotherapy** is used for the treatment of extensive and chronic AA mainly when the topical or intralesional corticosteroid injections are ineffective (Wang et al. 2012). Immunotherapy is one of the most used treatments of AA, where it is used since 1983, although it has a lot of side effects such as generalized eczema, contact dermatitis, urticaria, and lymphadenopathy. Another pulsed therapy is the use of topical 0.1% cream triamcinolone from Monday to Friday plus clobetasol propionate 0.5% ointment for Saturday and Sunday with a good result. There is no response to topical pimecrolimus cream and anthraline 1% cream (Torchia et al. 2010).

- **Pulsed systemic corticosteroids** are mainly used for two reasons.
  - To prevent or avoid long side effects of corticosteroids and,
  - To reduce underlying inflammatory process.

Prednisolone can be used for children in a dose of 0.5 mg/kg/month for a 3 months treatment till the age of 11 years, and 300 mg/month for 3 months for age 12-18 years. Methylprednisolone can be considered as one of the most used corticosteroids; hypokalemia and arrhythmia are the most dangerous side effects which limit its use, where 66% of patients with AA show only 30% hair regrowth after one year of treatment (Wang et al. 2012). The growth retardation and the reduction of bone mineral density and metabolic dysregulation limit the use corticosteroids including the oral use, where one of the most used one is oral methyl prednisolone in a dose of 0.5-0.8mg/kg/day, therefore the tapering of the dose is very important.
• **Dithranol:** The main mechanism of action of dithranol is by inhibition of the Th1 immune reaction. Its main important points preventing its use are dermatitis and staining of the skin and cloths when it falls on them. It is used in a concentration of 0.2%-0.5% for at least 3 months in the form of cream or ointment.

• **Phototherapy:** some studies considered UVA therapy not as a first line therapy where the use of UVA in children may be not beneficial because of its side effects such as increase in the possibility of skin cancer. Some studies show that there is a complete hair regrowth in children of 11 years with AU after 3 months of PUVA therapy, with no recorded side effects and no recurrence after 6 months (Mukherjee et al. 2009). 308 nm Excimer laser is one of the beneficial therapies for AA, especially in those patients who show no response for the treatment with minoxidil and corticosteroids.

• **Immunosuppressive agents:** it can be used for children but it is very limited and there is a need for blood test because of its side effects. Topical calcineurin inhibitors are used for children with AA even when it is on the face, eyebrows, or eyelashes, because it has not a lot of side effects like steroids; it can be also used for other skin diseases like psoriasis, dermatitis, etc. Methotrexate, azathioprine and cyclosporine as immunosuppressive drugs can be used for AA showing that the use of MTX in children gives only 38.4% response after more than 14 months of treatment, and more than 52% by the use of 2mg/kg/day.

• **Topical retinoids** can be used in the treatment of AA alone or in combination with other drugs.

• **Prostaglandin analogues** convert telogen to anagen stage, like latanoprost and bimataprost, which belong to the group of prostaglandin F2α analogues. Those drugs are not used for AA in children.

• **Biologics** are not recommended or used for the treatment of AA in children. A 15 years old girl who did not respond to topical pimecrolimus cream was treated with 0.1% cream triamcinolone Monday to Friday plus clobetasol propionate 0.5% ointment Saturday and Sunday. Both showed good results, but no response to 0.1% anthralin cream (Torchia et al. 2010).
• **Holistic management:** One of the most important treatments for children with AA is the psychological support because the patient may suffer from anxiety and stress. This management needs a co-management psychiatrist, and therefore the use of anti-depressant drugs like paroxetine, with a hypnotherapy, emotional support, and selective serotonin reuptake inhibitor are useful for the treatment of AA for pediatrics (Wang et al. 2012).

• **Drug Combinations:** In a study by Wasserman et al. (2007) there are two ways of AA treatment according to the age of the patients. The treatment options of AA in children <10 years are anthraline, topical sensitizers, ultra-potent corticosteroids under occlusion, topical minoxidil 5%, and the treatment options for children >10 years are anthraline, topical sensitizers, ultra-potent topical corticosteroids under occlusion, topical minoxidil 5%, intralesional corticosteroids, oral corticosteroids, wig or other scalp covering (Ganjoo et al. 2013).

  o The **first line of treatment for children less than 10 years** of age is **minoxidil 5%** twice daily for 6 months with a mild potent **topical corticosteroid** (Wang et al 2012). The use of potent steroids is more effective than weak ones in moderate to severe AA. The use of 0.05% clobetasol propionate foam shows regrowth at least in 50% of patients with AT/AU, while just 29% patients respond to 0.05% clobetasol propionate ointment. It will be easy to use 0.1% mometasone furoate or 0.1% betamethasone valerate scalp lotion to avoid skin atrophy.

  o The **second line of therapy** should be short contact anthralin if there is no response after 6 months with minoxidil and topical steroids.

  o For those **more than 10 years** of age with AA less than 50% of scalp is treated with intralesional injections of triamcinolone acetinoide. **Intralesional corticosteroids** are used, when children are mainly afraid of its use because of pain. Therefore, it is limited in use, even though the pain can be removed or reduced by the use of ice, cold compress, ethyl chloride spar, distraction therapy, or by the use of **topical anesthetic creams,** such as lidocaine 2.5% and prilocaine 2.5% mixture (EMLA); another mixture is ELA-Max cream (without prilocaine) which has the same efficacy of ELMA (Wang et al. 2012).
When there is no response after 6 months, then 5% topical minoxidil is used twice daily, with a potent topical corticosteroid and short contact anthralin. It is considered that the use of topical corticosteroids is more beneficial and useful, such as topical use of 0.2% fluocinolone acetonide cream, betamethasone valerate, betamethasone dipropionate lotion, and clobetasol propionate ointment, although relapses may occur after treatment with corticosteroids. Good results of hair regrowth after treatment with betamethasone valerate foam are obtained in 27-61% of patients. Some patients may show tolerance for systemic corticosteroids by injection, other patients may respond to i.v. injections of methylprednisolone pulsed therapy within a month in children between 1 and 16 years old of age. Therefore, intralesional corticosteroids are more useful; also there is hair regrowth seen in patients when treated with oral form of corticosteroids as a pulse therapy (Mukherjee et al. 2009).

- Another study shows that for the first line of therapy tincture iodine and anthralin are preferred. Also physiological treatment is considered as one of the most important supporting therapies for patients especially those who are under stress and anxiety. The long use of systemic corticosteroids may be dangerous because of its side effects (Seetharam et al. 2013).

11- DOCUMENTATION

The chart used for the documentation of total information of the disease history and the information of AA patients is as follows:

- Essential background data
- Patient’s initials
- Date of intake
- Age (Date of birth)
- First episode of AA (age, month/year of onset)
• Current episode AA: Age of onset, Month/year of onset, Duration of current episode (months)
• Extent of hair loss
• Sex (Male, Female)
• Racial group: Native, Color of the skin, Hispanic, White, not of Hispanic origin
• Predominant hair color (black, brown, red, blond, gray, white)
• Prior history of AA: Number of prior episodes of AA, History of AT or AT/AU at any time,  
  > 2 years’ duration, < 2 years’ duration
• Pertinent, immediate, past history
• History of infections within 6 months before onset of hair loss
• Initial episode of AA: Site of infection, Type of infection
• Current episode of AA: Site of infection, Type of infection
• History of vaccination within 6 months before onset of hair loss
• Initial episode of AA: Type of vaccination
• Current episode of AA: Type of vaccination
• Patient’s or parent’s perception of trigger for hair loss

12- NEW COMBINATION THERAPY FOR THE TREATMENT OF ALOPECIA AREATA

My hypothesis is the use of a new combination of drugs in one dose, and using these combined  
drugs with other drugs in form of a pulse therapy of corticosteroids. This way of treatment can  
be used in patients with all types of alopecia involving AA and also for the severe types AT and  
AU.

12.1- Indication:

The combination therapy, which is mentioned as follows, can be used for the treatment of AA,  
AT and AU, and also androgenic alopecia. It can give good results of regrowth of hairs and  
reduction of the hair patches of AA in different positions on the body. The response to this
combination therapy required studies on bioavailability, and physical and chemical assays to improve the usefulness and effectiveness of it.

12.2- Composition of the Formulas:

12.2.1. First Formula

The first formula consists of:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minoxidil solution 5%</td>
<td>120 ml</td>
</tr>
<tr>
<td>Retinoic acid (Vitamin A) 0.05% (RETIN .A) 0.5%</td>
<td>3 g</td>
</tr>
<tr>
<td>Betamethasone valerate 0.1% cream</td>
<td>15 g</td>
</tr>
<tr>
<td>Salicylic acid 1%</td>
<td>1 g</td>
</tr>
</tbody>
</table>

--------------------------------------------------

as a solution 200 cc composition of the drug.

This combination formula is to be given as 4 ml twice daily every day for 3-months until the patient responds to the treatment. When there is a response to this formula then we can complete the therapy for the next 3 months if necessary. It will be expected that the patient may suffer of redness and burning sensation due to salicylic acid. Due to its side effects this therapy should be taken with care during pregnancy and lactation because of the involvement of betamethasone.

12.2.2. Second Combination Formulation:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone valerate solution 0.1%</td>
<td>40 ml</td>
</tr>
<tr>
<td>Salicylic acid solution 10%</td>
<td>30 ml</td>
</tr>
<tr>
<td>Clotrimazole solution 1%</td>
<td>30 ml</td>
</tr>
</tbody>
</table>

--------------------------------------------------

as a solution of 100 ml
This combination therapy is to be given every 4 days where it should be applied on the patches for 3 hours before removing it. It should be used as long as the first combination is used. At the beginning of the therapy, it will be better when an intrallesional topical injection of methylprednisolone in a dose 4 cc twice daily is applied on the patches of AA, and to be left for more than 30 min every time on the skin.

12.3 Duration of Treatment:
This drug combination can be used for the first 3 months and then the next 3 months if there was a response to the drug treatment, represented by the regrowth of hair follicles or reduced size of patches. The use of minoxidil alone in a concentration of 5% can be continued after the regrowth of hairs for 3 months or longer, dependent on the severity of side effects. If there is not any benefit with this method, it will be better when it will be stopped and changed to the method of treatment as mentioned above.

12.4 Expected Side Effects:
As these combined drugs involve corticosteroids, there will be a chance of the side effects of steroids to be seen. When the side effects are severe, then it will not be used anymore and the patient has to consult the doctor in order to avoid worsening of his situation.

12.5 Contraindication:
This combination therapy is not suggested for pregnant women, during lactation or for nursing mothers, and also not for children younger than 12 years due to the contraindication of corticosteroids and/or one of the contents of this drug combination. During the therapy period the physician should give a big attention to the clinical aspects of patients with AA, because their blood and tissue were used for clinical investigation. To investigate the type of AA, extent and duration of hair loss or the presence of other genetics, clinical or immunological factors which may affect the end results of the therapy.

The other combination therapy for the treatment of AA is explained in the following diagram.
Chart (3) A new plan to treat AA
12.6- Treatment Plan with New Formulas according to Age and Extent of Hair Loss:

- Children **less than 12 years** old can be treated with topical solution of minoxidil 3% twice a day for 3 months in combination with topical corticosteroids which are applied before minoxidil to be left on the scalp for 30 min, then minoxidil for more than 30 min, and then washed up. If the response is good and the hair begins to appear it will be continued for 3 months with minoxidil 3% or 5%.

- Patients **more than 12 years** old can be treated as follows:
  - If the involvement of scalp is **less than 50%**, it will be treated with intralesional corticosteroids like triamcinolone acetonide (2.5-10mg/ml in a volume not more than 3 ml) in a single injection, repeated 4-6 weeks, or by using methylprednisolone 500 mg for 3 consecutive days monthly till 3 months, with topical corticosteroids like betamethasone or clobetasol 0.05% twice a day for 3 months. Then this procedure is followed by the use of minoxidil 5% as a topical solution for 3 months. If there is a good response then the treatment is continued with minoxidil 5% with topical clobetasol 0.05% for the next 3 months. If there is no response it will be better to use a combination formula as mentioned above.

  - If the involvement of scalp is **more than 50%** then the patient will be treated with the first and second combination formula.
    - If the response is good and accepted then complete the treatment with immunotherapy or with minoxidil 5% for the next 3 months.
    - But if the result is not accepted, it will be better to use the first combination new formula for the next 3 months. If there is no response it will be better to return to the physician. If the result is good then it will be better to stop the combination therapy and change to minoxidil for the next 3 months till a full regrowth of hair is observed.

12.7- Important Points in the Treatment of AA:

- Dermatography (tattooing) can be used to simulate eyebrows that have fallen out.
✓ Counseling is sometimes helpful for people who find it difficult to cope with hair loss.
✓ Remember to use sunblock or a hat to protect bald patches when the patient is out of the home.

13- SUMMARY

There are a lot of drugs that can be used for the treatment of AA like corticosteroids (systemically or topically), minoxidil, immunotherapy, prostaglandin analogues, topical retinoids, sulfasalazine, PUVA, excimer laser, methotrexate, cyclosporine, azathioprine, garlic gel, topical contact sensitizer, topical onion gel, imiquimod, cacineurin inhibitors, botulinum toxin, photodynamic therapy as well as biological and psychological support.

In this study, I tried to explain the main ways of treatment that can be of benefit, mentioning also a new way of the treatment, which includes the same available drugs that have been already used for the treatment of AA, but with a new idea of combination of drugs, which may be more useful and effective. This study is just a theoretical study, which could be of benefit in the future in the search of more effective and useful drugs.

This study is to explain the main important information about AA including definition of AA, history, histopathology, causes, diagnosis, and symptoms, AA in children, and the treatment options of AA. AA itself does not damage the general health and thus will not lead to any general health problems without treatment. When considering any treatment choices, we should take into account the possible side-effects that some of the drugs may have. Also, treatment promotes hair to re-grow, but do not affect or cure the underlying cause of the condition. The main drugs used for the treatment of AA are:

- Intralesional steroids as triamcinolone acetonide
- Medicines applied to the skin including corticosteroids, immunotherapy, and minoxidil
- Ultraviolet light therapy

In this master thesis I presented a new two combination formulation which may need more studies for proving its efficacy, even though its components are widely used by physicians. I
thought that we can combine these drugs in one fixed combination that may be more effective and the hair regrowth could be seen in a short period of time (3 months), or more than that depending on the extent of the patches and the presence of other diseases which may limit the use of it. As I was in Iraq I had got this idea and I had proposed it for many physicians who began to prove it on patients who accepted to be a volunteer. Most of the patients had good results within 3-4 months, with no relapse after stopping the treatment. I wish that the study on bioavailability and efficacy could be completed soon. I would be then so happy if the formulation will be certified and accepted.

In comparison with other methods, this method can be considered of benefit and effectiveness for the treatment of alopecia areata. Most of the patients in Iraq showed a good response to the treatment with few side effects comparing to those patients who were treated with a single method of therapy or in a combination with other drugs just like minoxidil alone or with systemic steroids, intrallesional steroids.
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