Background: Although research over the last few years has yielded valuable data on the etiology and pathogenesis of the insidious form of hair loss in alopecia areata, there are still many grey areas, and the answers of many unfathomable questions continue to elude scientists and medical experts. With an enigmatic etiology, there is neither a permanent cure for AA nor a universally proven therapy inducing remission.

Objective: This study aims to showing the efficacy of topical PUVA-SOL in the treatment of alopecia areata, and immunomodulatory effect of topical PUVA-SOL therapy.

Patients And Methods: One hundred and fifty patients with AA attending Department of Dermatology at Tikrit Teaching Hospital were enrolled in this study in the period December 2008 through to December 2009; there were 100 cases (66.66%) and 50 controls (33.33%). All patients were examined clinically, then interviewed and detailed AA questionnaires were completed for each of them. All patients included in this study suffered from AA, which failed to respond to conventional therapy. Patients were instructed that they should stop all medications at least 3 weeks before starting therapy with trisoralin (Trimethyl psoralen) 0.15 topical application. After 15 minutes of topical psoralen, the patients were instructed to expose the affected skin to sunlight.

Results: The most common site for AA found in the scalp. The AA more common in male than female, and more common in the young age than old age. The response of lesions to treatment were 68% in the cases, and 13% in the control while not response 32% in the cases, and 87% in the control. The time of response to treatment more

Rezumat
Introducere: Deși cercetările din ultimii ani au adus contribuții valoroase la înțelegerea etiologiei și patogenezei formei insidioase de cădere a părului în alopecia areata, încă persistă numeroase zone grele și multe întrebări nu și-au găsit decamătate răspunsurile din partea oamenilor de știință și specialiștilor în medicină. Având o etiologie încă incomplet cunoscută, AA nu beneficiază de cură permanentă și nici de o terapie universal acceptată, capabilă să producă remisie.

Obiectiv: Studiul de față urmărește să demonstreze eficacitatea tratamentului topical cu PUVA-SOL în alopecia areata și efectul imunomodulator al terapiei cu PUVA-SOL topical.

Pacienți și metode: O sută cincizeci de pacienți cu AA aflați în tratament la Spitalul Universitar Tikrit, Secția de Dermatologie, au participat la acest studiu desfășurat între decembrie 2008-decembrie 2009; grupul experimental a fost format din 100 de pacienți (66,66%) iar grupul de control a constat din 50 de persoane (33,33%). Toți pacienții au fost examinați clinic, apoi interviuau și au fost completeate chestionare AA detaliate. Toți pacienții incluși în acest studiu suferea de forme de AA care nu au răspuns la terapii convenționale. Pacienților li s-a cerut să întrerupă orice medicatie pentru o perioadă de cel puțin 3 săptămâni înainte de a începe terapia cu trisoralin (Trimethyl psoralen) 0,15 aplicat topical. La 15 minute după aplicarea psoralenului topical, aceștia au fost instruiți să își expunea zonele afectate ale pielii la soare.

Rezultate: Zona afectată cu predilecție de către AA este scalpul. AA este mai frecvent la bărbuți decât la femei și la tineri comparativ cu vârstnicii. Răspunsul la tratament a fost pozitiv în 68% din cazurile din grupul experimental și în 13% din grupul de control. Tratamentul nu a dat rezultate în proporție de 32% în grupul...
Introduction

The characteristics of the hair loss disease we now know to be alopecia areata (AA) were first described by Cornelius Celsus in 30 A.D. Celsus described two forms of alopecia, using the Greek word alopekia, literally translating as ‘fox mange’. However, the actual term ‘alopecia areata’ was first used by Sauvages in his ‘Nosologica Medica’, published in the eighteenth century (1).

Alopecia areata (AA), is a common asymptomatic disease characterized by the rapid onset of total hair loss in a sharply defined, usually round, area. Any hair-bearing surface may be affected (2).

A typical patch is uninfamed, with no scaling, but with empty hair follicles. Pathognomonic ‘exclamation-mark’ hairs may be seen around the edge of enlarging areas. They are broken off about 4 mm from the scalp, and are narrowed and less pigmented proximally (3).

Alopecia areata accounts for about 2% of new dermatological outpatient attendances in Britain and USA. Children and young adults are most frequently affected, and there is a positive family history in 10-25% of cases (4). Anywhere between 7% and 66% of people with AA also have aberrant nail formation depending on which reports you read (Muller 1963, Baran 1984). It has also been observed after psychological stress. Links with endocrine disturbances, particularly of the thyroid, have not been confirmed, and the same applies to focal infections (7).

The pathophysiology of AA remains unknown. The most widely accepted hypothesis is that AA is a T-cell-mediated autoimmune condition that is most likely to occur in genetically predisposed individuals (8). A minority of dermatologists dispute the idea of AA being an autoimmune initiated disease. Using PCR (polymerase chain reaction) methods, gene sequences that code for cytomegalovirus (CMV) have been found in skin biopsies taken from people with AA (Skinner 1995a, Skinner 1995b). In comparison, biopsies from the general population were shown not to contain similar CMV genes. The work is at the preliminary stage but the researchers are suggesting that CMV may be present in hair follicles and that the immune system is mounting a normal response against the virus to get rid of it. In doing so it also disrupts and destroys adjacent hair follicle tissue (9).

It is not at present possible to attribute all or indeed any case of AA to a single cause. Among the many factors which appear to be implicated in at least a proportion of cases are the patient’s genetic constitution, the atopic state, non-specific immune and organ-specific autoimmune reactions and possibly emotional stress (6). The idea of genetic influences is supported by its occurrence in families and its association with certain congenital diseases such as trisomy 21 (Down’s syndrome) or Vogt-Koyanagi syndrome. It has also been observed after psychological stress. Links with endocrine disturbances, particularly of the thyroid, have not been confirmed, and the same applies to focal infections (7).

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the inflammatory scarring alopecias, little or none of the inflammatory infiltrate is seen around the isthmus of the hair follicle, the site of hair follicle stem cell. This may be explain why follicles are not destroyed in AA (10).

The preponderance of evidence supports an autoimmune etiology. Oligoclonal and autoreactive T-lymphocytes are present in the peribulbar inflammatory infiltrate, and many patients respond to immune-modulating drugs. Affected alopecia areata scalp skin grafted onto nude mice with severe combined immunodeficiency demonstrates loss of infiltrating lymphocytes and hair growth. In this model, injecting T-lymphocytes with scalp homogenate can produce the alopecia. Follicular melanocytes substitute for scalp homogenate to produce alopecia areata in this model, providing evidence that follicular melanocytes are the targets for activated T-cells in this disease. This hypothesis is also supported by the observations that white hair is rarely affected and regrowing hair is often depigmented (11).

At present, all treatment are palliative, only controlling the problem; they certainly do not cure the condition (12). No curative treatment is currently available. Treatment for AA is unsatisfactory (13).

The mechanism of action of PUVA in AA is believed to be a photo-immunologic action. It may affect T-cell function and antigen presenting and possibly inhibit local immunologic attack against the hair follicle by depleting Langerhans cells (14). The psoralen administered either topically or orally and is followed in 1 or 2 hours with UVA. Treatments are administered 2-3 times a week with a gradual increase in UVA dosage (15).

Localized PUVA therapy is effective in some cases, but once hair regrowth begins, further therapy is compromised as the light does not reach the scalp. More recent data have shown total-body PUVA to be somewhat effective in growth of scalp hair (16).

PUVA is a type of phototherapy used as an immunomodulatory treatment for severe and recalcitrant skin diseases such psoriasis, vitiligo as well as alopecia areata (17).

At present, all treatment for AA are palliative, only controlling the problem; they certainly do not cure the condition. Treatment options can be divided into four main areas.

1. Non-specific irritants; e.g. dithranol and phenol.
2. Immune inhibitors; e.g. systemic steroids, PUVA, and cyclosporine.
3. Immune enhancers; e.g. contact dermatitis induction, inosiplex.
4. Of unknown action; e.g. minoxidil.

1. Non-specific irritants: anthralin (antimitotic effect) is used in the treatment of AA in concentration of 0.25%-1% . It may have a non-specific immunomodulatory effect eliciting hair re-growth. Cosmetically acceptable re-growth has been reported to vary from 20%-25% (18). Garlic has been used in the treatment of AA, but there are no much studies (19). And most recently an Iraqi study showed that onion juice is an effective treatment in AA in comparison with tap water (20).

2. Immune inhibitors:

A- Steroids: the mode of action of corticosteroids is probably through their anti-inflammatory and immunosuppressive effects (21). Systemic corticosteroids will restore normal hair growth in many cases of AA. Most cases relapse at some stage during or after withdrawal of treatment. Intralesional steroids is the first line therapy for adult patients with less than 50% scalp involvement. Topical corticosteroids have been reported to have some effect in the treatment of AA but overall topical corticosteroids used as a monotherapy are probably ineffective (22).

B- Photochemotherapy: the mechanism of action of PUVA in AA is believed to be a photo-immunologic action. It may affect T-cell function and antigen presenting cell and possibly inhibit local immunologic attack against the hair follicle by depleting Langerhans cells (23).

C- Cyclosporin: because of their side effects profile, high recurrence rate after discontinuation of the treatment, long treatment periods, and inability to change the ultimate prognosis of the disease, this treatment is simply not practical in AA (24).

D- Tacrolimus (Topical FK506, Prograf): topical FK506 is an immunosuppressive agent and an antibiotic macrolid that like cyclosporine A, is a specific immune cell inhibitor. The potential therapeutic efficacy of topical FK506 was studied in a rate model of AA. Results sowed
that hair growth occurred at the site of drug application within 2-3 weeks and growth continued for 3 weeks beyond termination of treatment after which gradual hair loss was observed (25).

3. Immune inducers:

A- Topical immunotherapy. The mechanism of action of topical immunotherapy is unclear. The immunomodulatory effect of the topical sensitizers is supported by a decrease in the peribulbar CD4/CD8 lymphocyte ratio. Shift in the position of the T-lymphocyte away from Perifollicular areas to the interfollicular areas and dermis (26). Three contact sensitizers have been used in AA: dinitrochlorobenzene (DNCB), squaric acid dibutyl ester (SADBE), and diphenylcyclopropenone (DPCP). Because of the mutagenic effects of DNCB, it is now less used (27).

B- Inosiplex: it was reported there is a success with oral inosiplex but the effect was lost within 2-3 weeks of cessation. However, only partial growth was seen, but growth was maintained in the majority after cross over to placebo (28).

C- Zinc sulphate: zinc sulphate has been used in dermatology as an immunomodulator, and it was effective in the treatment of viral warts, and cutaneous leishmaniasis (29).

D- BCG: Bcellus Calmete Guerin (BCG) as a vaccine was introduced as a prophylactic agent against tuberculosis, and it also has been used in the treatment of malignant melanoma, viral warts, herpes simplex facialis and genitalis to enhance the immunity in these diseases, so it might act as an immunomodulators in these diseases. In AA, BCG immunotherapy was found to be an effective mode of treatment (69%), and the response was much higher in patients with ordinary patchy AA compared with the other forms of AA (30).

E- Thymopentin:thymopentin is a synthetic pentapeptide corresponding to the active structural of the natural 49 amino acids containing thymic hormone thymopentin which has shown impressive immune-regulatory activity in many model systems and human in vitro tests. It has been used in the treatment of AA in a dose of 50mg subcutaneously for 10 weeks. It requires further studies for confirmation of their efficacy (31).

F- Interferon alpha (INF-á): Intralesional IFN-á has been used in the treatment of AA ranging from patchy disease to alopecia universalis. The treatment was used on selected area of alopecia. Follow-up at 3 months revealed local terminal hair growth and regional lymphadenopathy, and treatment schedule used had no significant effect on AA (32).

4. Others:

A- Minoxidil: minoxidil is a biologic response modifier that enhances hair growth. Minoxidil stimulate follicular DNA synthesis, has a direct effect on the proliferation and differentiation of follicular keratinocytes in vitro, and regulate hair physiology independently of blood flow influences. Its mode of action is unknown, but it does not have an immunomodulatory effect. Cosmetically acceptable hair regrowth in patients with AA using topical minoxidil solution has been shown to be approximately 20-45% of patients with 20-90% scalp involvement (33).

B- Electrotherapy: this method of treatment of treating patchy AA by using small DC current 10 milliamper, 40 voltage and show that electrical stimulation is safe and effective mode of therapy in AA (34).

Patients and methods

One hundred and fifty patients with alopecia areata attending Department of Dermatology at Tikrit Teaching Hospital were enrolled in this study in the period December 2008 through to December 2009. There were 100 cases and 50 controls.

All patients were examined clinically, then interviewed and detailed AA questionnaires were completed for each of them. All patients included in this study suffered from AA, which failed to response to conventional therapy.

The exclusion criteria are:

1. Patients under age of 14 years.
2. Patients with personal or family history of malignant melanoma.
3. Patients with evidence of light aggravated diseases, hepatic or renal impairment, cataract, pregnant and lactating women.
4. Patients who take important drugs (chemotherapy, steroids).

Patients were instructed that they should stop all medications at least 3 weeks before starting therapy with trisoralin (Trimethyl psoralen)
0.15% topical solution. After 15 minutes of topical psoralen, the patients were instructed to expose the affected skin to sunlight and he/she should wear goggles. The treatment given 3 times/week (every other day). First day of treatment was exposed for 5 minutes, then increased to 10 minutes at the second session, 15 minutes at the third session, 20 minutes at the fourth session, then continue on 20 minutes for the rest of the session. The patient should sit in open area (not inside room), the time of exposure should be between 3.00-4.00 pm. After the exposure to the sunlight, the patient stay indoor for the remainder of the day.

**Results**

One hundred fifty patients were included in this study, which is divided into two groups the first group (cases) and equal 100 (66.66%) while the second group (control) equal 50 (33.33%) as show in the table (1).

The site of lesions mostly found in the scalp as show in the table (2). The AA more common in male than females as show in the table (3), and more common in young age than old age as show in the table (4).

The number of lesions according to the gender, in the male 218 (65%), in the female 116(35%)as show in the table (5). This indicate the number of lesions in the male more than female.

The response of lesion cases and controls to treatment, the cases which is response and equal 150 (68%) while cases not response equal 70(32%). The control which is response equal 15 (13%) while control not response 99 (87%) as show in the table (6).
The response of cases and controls to treatment according to time. The response more visible after 20 weeks in the cases and controls as show in the table (7).

Discussion

Alopecia areata is a non-scarring, recurrent hair disorder occurring in 1 to 2% of the population and affecting both sexes in all racial groups. Although AA is not life threatening, the pressures of an image orientated society can make hair loss psychologically devastating for those affected, their families, and friends.

There is no cure for this mysterious form of hair loss, and the key challenge of managing AA lies in finding a treatment regimen that really works (35). The new biologic agents (Etanercept, Infliximid, Efalizumab, Alefacept) are proteins that possess pharmacologic activity and can be extracted from tissues or synthesized through recombinant DNA techniques are proved in use in several countries for treatment of refractory rheumatoid arthritis and psoriasis. However, because some treatment modalities that have been successful in treating psoriasis have also been effective in treating AA, clinical trials of the use of biological drugs in AA may help define a universally acceptable form of treatment of patchy hair loss (36).

PUVA-SOL is used with patients who cannot go to PUVA facilities, the doctor may prescribe psoralen to be used with natural sunlight exposure. The doctor will give the patients careful instructions on carrying out treatment at home and monitoring the patient during scheduled checkup. PUVA has been used with variable success in the treatment of AA. PUVA may be an effective treatment through its photo-immunologic effect on T cells. The immunosuppression induced by PUVA therapy can be attributed to different mechanisms (38):

1. The disappearance of epidermal Langerhans cells and their decreased antigen-presenting capacity.
2. Induces apoptosis (programmed self death) in T lymphocytes.
3. Has also been shown to influence the release of cytokines.
4. Because dendrite cells are thought to play an important role in the initiation of AA, PUVA might exert an inhibitory effect on the development of this form of hair loss.
5. PUVA has been sown to stimulate the Dopa-negative melanocytes in the outer root sheath to divide and proliferate. As melanocytes appear to be playing important role in AA.

In present study one hundreds and fifty patients were included with confirming diagnosis AA were performed. The patients were divided into two groups, the first group were 100, while the second group (control) were 50.

AA most common site was scalp (86.66%); and more common in male (58.66%) than female, and young age than old age. Also in our study take the numbers of lesions in all subject study were 334. The response to treatment were 68% in the cases, and 13% in the control while not response 32% in the cases, and 87% in the control. The time of response to treatment more visible after 20 weeks of treatment among cases and control.

With an enigmatic etiology, there is neither a permanent cure for AA nor a universally proven for inducing remission. Early intervention is crucial, and most patients can be offered hope and support to help them cope with the months of treatment usually needed to achieve
reduction in disease symptoms. In any dermatological condition, the ideal treatment would be one that is effective, easy to apply, painless, free of side effects, and inexpensive-therapy should always be commenced with the treatment module that fulfills as many of these criteria as possible.

Topical and natural sunlight showed little side effects in the current study during the period of therapy in comparison with steroid that cause skin atrophy and other side effects of systemic steroids. The presence of sunlight approximately all over year in our country encourages us to use sunlight instead of UVA lamp which is easier and cheaper for patients.

Alopecia areata is difficult to treat and few treatments have been tested in randomized, controlled trials. The tendency to spontaneous remission and lack of adverse effects on general health are important considerations in management, and counseling, in many cases. Alopecia areata may cause considerable psychological and social disability and, in some cases, particularly those seen in secondary care, it may be a chronic and persistent disease causing extensive or universal hair loss. If the prognosis is poor (e.g. in a prepubertal atopic child with total alopecia), a full explanation and help adjusting to the problems of hair loss will be of far greater value than the raising of unwarranted hopes.

Hopefully, once the trigger for AA is identified, more specific, more effective and better tolerate treatments will be developed.

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Bibliography
2. Thomas P. Habif; Clinical Dermatology; 5th ed; British Library Cataloguing in Publication Data; 2010; 932.
3. J.A.A.Hunter, J.A.Savin, M.V.Dahi; Clinical Dermatology; 3rd ed; Blackwell Science; 2002; 164.
11. William D James, Timothy G Berger, Dirk M Elston; Andrew’s Diseases of The Skin, Clinical Dermatology; Tenth Edition; 2006; 750.
27. Summer K & Goggelmann W. I-Chloro-2,4-dinitrochlorobenzene depletes glutathione in rat skin is mutagenic. Mutant Res, 1980; 77; 91-93.
30. Al-Samarrai A. BCG Immunotherapy in alopecia areata. Diploma dissertation, Department of Dermatology, College of Medicine, University of Baghdad; 1995; 24.

Conflict de interesse
NEDECLARATE

Conflict of interest
NONE DECLARED