F028 High Yield Hair Cases
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Objectives

Following completion of the session, participants should be able to:
- Recognize important features from a patient's history and scalp exam to suggest a diagnosis of hair loss
- Recognize important features of a scalp biopsy
- Choose appropriate treatments

QUESTION 1. Trichoscopy of the crown in a 28 year old male is shown in the photo. This male may be at increased risk for which of the following?

A. Prostate cancer
B. Metabolic syndrome
C. Skin cancer
D. All of the above

CORRECT ANSWER: D. All of the above.

COMMENTS AND DISCUSSION

This dermatoscopic (trichoscopic) image shows a variation in the caliber of follicles – a feature that is known as “anisotrichosis”. Anisotrichosis is a typical feature seen in individuals with androgenetic alopecia (AGA). AGA is associated with a progressive miniaturization of hairs from thick 60 um (or thicker) so called “terminal hairs” into thinner and thinner hairs (i.e. miniaturizing hairs) and eventually extremely thin and short “vellus” hairs. This terminal-to-vellus transformation leads to the phenomenon of anisotrichosis.
Androgenetic alopecia is associated with an increased several disease associations include prostate cancer, metabolic syndrome and skin cancer.

A. Prostate Cancer
A number of studies have suggested that males with some patterns of balding are at increased risk to develop prostate cancer. A new large meta-analysis of all eligible cohort and case-control studies examined the risk of prostate cancer in males with various types of balding. 15 studies were included in the meta-analysis study. Overall, a slight but statistically significant association was observed for vertex baldness (RR 1.24, 95% CI 1.05-1.46) but not for other types of baldness. More studies are needed to confirm these findings and to better understand exactly why vertex balding specifically carriers this increased risk.

B. Metabolic syndrome
Metabolic syndrome refers to a constellation of symptoms and signs such as abnormal cholesterol, high blood pressure, diabetes and obesity that increase one’s risk of heart disease. Numerous studies have suggested that both men and women with androgenetic alopecia are at risk for metabolic syndrome.

A 2016 meta-analysis by Kim and colleagues, for example, evaluated 19 previous studies. A statistically significant difference in lipids was observed in patients with androgenetic alopecia compared to controls.

C. Skin cancer
Patients with androgenetic alopecia are at increased risk for skin cancer. Some of the risk is attributed to the reduction in the ultraviolet radiation blocking ability of the hair but some of the risk may also be due to the genetics that governs androgenetic alopecia too.

A 2016 study by Wen-Qing et al was one of the first prospective study to report the associations between male pattern baldness and risk of incident skin cancer. The authors found that male-pattern baldness was significantly associated with increased risk of both SCC and BCC. In contrast, male pattern baldness was not significantly associated with risk of melanoma ‘overall’, but was associated with an increased risk for SCC and melanoma of the scalp.

References
Wen-Qing et al. Male pattern baldness and risk of incident skin cancer in a cohort of men. Int J Cancer 2016; 139 (12); 2671-2678
Question 2. Trichoscopy of a 25 year old male of Afro-Caribbean descent is shown. Which of the following treatments should be considered as a first-line treatment?

A. Tofacitinib  
B. Adalimumab  
C. Isotretinoin  
D. Prednisone

CORRECT ANSWER: C, Isotretinoin

COMMENTS AND DISCUSSION

The trichoscopic image shows a ‘sinus tract’ from a patient with the neutrophilic scarring alopecia known as dissecting cellulitis. Dissecting cellulitis is a neutrophilic scarring alopecia that more often affects young men age 20-40. Patients present with tender nodules some of which drain pus or serosanginous fluid. Any area of the scalp may be affected including the crown and occiput. Cultures are often sterile.

The precise cause of dissecting cellulitis is not clear. A defect in the keratinization of the hair follicle wall has been proposed which leads to collapse of the hair follicle and secondary infection. About 25-30% of patients also have various components of the so called follicular occlusion tetrad which includes hidradenitis suppurativa, acne conglobate, and pilonidal cysts. Isotretinoin, which affects keratinization is viewed as a first-line agent in management of this disease.
A. Tofacitinib (Incorrect). The janus kinase inhibitor tofacitinib is not thought to have a role in management of dissecting cellulitis.

B. Adalimumab (Incorrect). The TNF inhibitor adalimumab certainly may be helpful in the management of dissecting cellulitis but would not be a “first-line” agent. It is more correctly viewed as a second line agent.

C. Isotretinoin. Isotretinoin, which affects the keratinization of the hair follicle, is viewed as a first-line agent in treatment of dissecting cellulitis. Treatment for dissecting cellulitis may be challenging. A 2018 study by Lee and colleagues showed that approximately 37% of patient treated with isotretinoin achieve remission.

D. Prednisone (Incorrect). Prednisone can help some patients with extremely painful and progressive nodules. It is best viewed as an adjunct therapy for some patients rather than a first line treatment.

Reference

Question 3. A 56 year old female presents with eyebrow loss and scarring alopecia of the frontal hairline. Dermoscopy shows perifollicular scale. Which of the following statements regarding perifollicular scale is most accurate?

A. Greater amounts of perifollicular scale may be associated with greater inflammation on histology  
B. Perifollicular scale is more common in the sideburns than the frontal hairline  
C. Perifollicular scale correlates with disease duration  
D. All of the above

CORRECT ANSWER: A, Greater amounts of perifollicular scale may be associated with greater inflammation on histology

COMMENTS AND DISCUSSION

Eyebrow loss and scarring alopecia of the frontal hairline in a 56 year old female must raise suspicion for frontal fibrosing alopecia (FFA). Trichoscopy of the hairline in patients with FFA shows several features include absence of vellus hairs, perifollicular scale, perifollicular erythema, and acquired pili torti. The findings of perifollicular scale and erythema are more commonly seen in the forehead region than in the pre-auricular and sideburn areas. In fact, the pre-auricular and sideburn areas in patients with FFA often mimic the appearance of alopecia areata because the scale and redness are often absent – of at least less severe than the frontal hairline.

A. Greater amounts of perifollicular scale may be associated with greater inflammation on histology (correct).

Recent data over the last few years has suggested that several dermatoscopic findings in patients with the scarring alopecia frontal fibrosing alopecia may be associated with the level of activity of the disease. For example, previous studies had suggested that redness around hairs (perifollicular erythema) was associated with a disease activity and a higher chance of disease progression.

Martinez Velasco and colleagues set out to evaluate the significance of perifollicular scale by studying 20 biopsies from patients with FFA. Their studies showed a good correlation between the amount of scale that was present around hair follicles and the degree of inflammation present under scalp.
B. Perifollicular scale is more common in the sideburns than the frontal hairline (incorrect). Perifollicular scale is less common in the sideburns than the frontal hairline in FFA. In fact, the sideburns in FFA often lacks scale and appears similar to alopecia areata.

C. Perifollicular scale correlates with disease duration (incorrect). Perifollicular scale correlates with disease activity but less so with disease duration. Some patients with long standing disease have scale but others do not. Perifollicular scale is less correlated with disease duration.

References


Question 4. What is the most likely organism isolated from the crown in this male patient with scalp burning, tenderness and hair loss?

A. S. aureus  
B. Candida albicans  
C. Malassezia spp.  
D. Herpes simplex

CORRECT ANSWER: A, S aureus

COMMENTS AND DISCUSSION

This dermatoscopic (trichoscopic) image shows scaling, crusting and compounding of follicles. The one centrally located follicle in the photo has 11 hairs emerging from a single ostia. Compound follicles are follicles with 6 or more hairs and are more commonly found in the neutrophilic scarring alopecias than the lymphocytic scarring alopecias. The follicle at the 12 o'clock position in the photograph is showing typically starburst pattern of scaling that is so typical of the disease. Compound follicles are seen in some patients with folliculitis decalvans and one variant of folliculitis decalvans where compound follicles predominate is known as ‘tufted folliculitis.’
A male with burning and tenderness in the crown whose trichoscopy shows “compound follicles” has folliculitis decalvans until proven otherwise. A biopsy, of course, would confirm the diagnosis of the neutrophilic scarring alopecia. A variety of organisms can potentially be isolated from the scalp in folliculitis decalvans. S. aureus, however, is most common.

**A. S. aureus (correct).** Staphylococcus aureus is frequently isolated from cultures taken from pustules in individuals with FD. Isolation of the bacteria, however is not required for the diagnosis. Among the more widely accepted theories of the pathogenesis of FD is the concept that FD is trigger by staphylococcal superantigens that bind major histocompatibility complex proteins (MHC class II) and in turn cause non specific activation of T cells. Such T cell activation in turn causes release of a variety of cytokines and facilitates destruction of hair follicles. Other mechanisms have also been proposed.

![Diagram](staphylococcal-super-antigens.png)

**B. Candida albicans (Incorrect).** This is an uncommon skin organism from the scalp.

**C. Malassezia (Incorrect).** Although Malassezia may contribute to a variety of skin issues, it is not implicated in this presentation.

**D. Varicella zoster virus (Incorrect).** Varicella zoster virus the cause of shingles. The presentation of compound follicles in a male with a long standing history of burning, tenderness would be unusual for the typically more acute presentation of herpes zoster.

Question 5. A 22 year old male presents with concerns about increased hair shedding. He is asymptomatic. Blood tests are normal and no new medications have recently been started. The patient is healthy. What is the most likely reason for his hair shedding?

A. Telogen effluvium
B. Androgenetic alopecia
C. Seborrheic dermatitis
D. Lichen planopilaris

CORRECT ANSWER: B, Androgenetic alopecia

COMMENTS AND DISCUSSION

There is a wide differential diagnosis of scalp shedding. Telogen effluvium is certainly among the most common conditions known to given hair shedding. Telogen effluvium may be caused by endocrine abnormalities, stress, nutritional issues, poor diet, iron deficiency and a range of internal illnesses. Androgenetic alopecia is also a cause of hair shedding and all too often forgotten as a cause of hair shedding in both males and females. In a healthy male with normal blood tests who presents with increased hair shedding, androgenetic alopecia must be considered at the top of the list.

A. Telogen effluvium (Incorrect). Telogen effluvium is most certainly a possible diagnosis for this male but likely not ahead of androgenetic alopecia given the information we have about a healthy male with normal blood tests. However, issues such as stress, weight loss, undiagnosed illnesses, sexually transmitted diseases, dietary deficiencies in minerals and micronutrients all need to be considered.

B. Androgenetic alopecia (correct). It is often forgotten that androgenetic alopecia is associated with increased hair shedding in the areas of hair thinning. Males frequently present in the early stages of androgenetic alopecia simply with hair shedding. Minor changes in the hairline may be seen at that time or may be missed or simply ascribed to hairline maturation. The default diagnosis for males and females with shedding must remain androgenetic alopecia.

C. Seborrheic dermatitis (Incorrect). Seborrheic dermatitis can cause shedding but unless it is severe it usually does not cause severe shedding. The amount of shedding in seborrheic dermatitis is usually correlated with the severity of the seborrheic dermatitis.

D. Lichen planopilaris (Incorrect). It is uncommon, albeit not impossible, for lichen planopilaris to be asymptomatic. The disease more typically presents with symptoms such as itching, burning or tenderness.

Reference

Question 6. A 34 year old female has developed severe itching and burning in the scalp. Examination shows scalp redness with some redness on the neck, eyelids, face and back. What is the most likely shampoo related allergen to cause this reaction?

A. Cocamidopropyl betaine.  
B. Propylene glycol  
C. MCI/MI  
D. Fragrance  

CORRECT ANSWER: D, Fragrance

COMMENTS AND DISCUSSION

Allergies to shampoos may present with a variety of different clinical presentations. Some patients have scalp symptoms but many develop a dermatitis only on the face, eyelids, ears, neck and back.

Fragrance is the most common allergen in shampoos. Of 179 shampoos analyzed in a study by Zirwas, 95 % had fragrance. It is estimated that 99% of the population comes into contact with fragrance allergens during the week and about 1-4 % of them have fragrance allergies. Fragrance allergies are believed to be increasing around the world.

Patients with fragrance allergy should look for products that are fragrance-free rather then 'unscented.' The term unscented is somewhat meaningless but does indicated that the product does not have a strong odor. However, an unscented product could still be full of fragrance but the fragrance helps dampen down some objectionable smell to create an overall more neutral smelling product. A patient with an allergy to fragrance could have a serious reaction to a product labelled unscented.

More and more countries around the world are mandating that manufacturers disclose fragrance ingredients and no longer simply use the term ‘fragrance’. Some countries are further ahead in this goal than others.

The most commonly found allergens in shampoos, in order are:

1. Fragrance – found in 95 % of shampoos according to Zirwas study  
2. Cocamidopropyl betaine – found in 53 % of shampoos  
3. MCI/MI – found in 51.4 % of shampoos  
4. Formaldehyde releasers - found in 48.6 % of shampoos  
5. Propylene glycol - found in 38 % of shampoos
A CLOSER LOOK AT FRAGRANCE-FREE SHAMPOOS

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Scalp sensitivities can rarely be from fragrance sensitivities. These can also cause reactions on the face and neck. A great majority of shampoos contain fragrance. The following are fragrance-free shampoos:

**OPTION 1: FREE AND CLEAR SHAMPOO**

- No fragrance
- No Parabens
- No SLS (sulphate)
- No CAPB

Ingredients: purified water, lauryl glucoside, coco-glucoside, acrylates copolymer, disodium cocoyl glutamate, sodium cocoyl glycinate, glycerin, sucrose cocoate, panthenol, pentylene glycol, 1,2-hexanediol, sodium cocoyl glutamate, disodium EDTA, caprylyl glycol, sodium hydroxide, sodium chloride
OPTION 2: DUCRAY PHYSIOPROTECTIVE SENSIINOL SHAMPOO

· No fragrance · No Parabens · No alcohol · No CAPB

**Ingredients:** WATER (AQUA), SODIUM LAURETH SULFATE, ZINC COCETH SULFATE, CETEARETH-60 MYRISTYL GLYCOL, LAURETH-9, COCO-GLUCOSIDE, 1,2-HEXANEDIOL, CAPRYLYL GLYCOL, CITRIC ACID, DISODIUM EDTA, HYDROXYPROPYL GUAR HYDROXYPROPYLTRIMONIUM CHLORIDE, SODIUM CHLORIDE, SODIUM HYDROXIDE

OPTION 3: AFM SAFE CHOICE HEAD AND BODY SHAMPOO

· No fragrance · No Parabens · No alcohol · No CAPB

**Ingredients:** Water, Sodium Laureth Sulfate, Cocamide DEA, Citric Acid.

OPTION 4: EXEDERM SHAMPOO

· No fragrance · No Parabens · No alcohol · No CAPB

**Ingredients:** Purified water, decyl glucoside, glycerin, xanthan gum, disodium cocoamphodiacetate, phenoxyethanol, caprylyl glycol, polyquaterium-10, guar hydroxypropyltrimonium chloride, EDTA, citric acid
OTHER OPTIONS FOR FRAGRANCE- FREE SHAMPOOS

5. CLINIDERM SOOTHING SCALP SHAMPOO

No fragrance, No Parabens, No formaldehyde... but has CAPB

Ingredients: Aqua, Cocamidopropyl Betaine, PEG-80 Sorbitan Laurate, Sodium Trideceth Sulfate, PEG-150 Distearate, Acrylates Crosspolymer-4, Butylene Glycol, Fumaria Officinalis Extract, 1,2-Hexanediol, Caprylyl Glycol, Tropolone, Sodium Hydroxide, PEG-20 Sorbitan Laurate, Citrus Aurantium Dulcis (Orange) Oil, Citrus Nobilis (Mandarin Orange) Peel Oil, Citrus Medica Limonum (Lemon) Peel Oil, Citrus Aurantifolia (Lime) Oil, Vetiveria Zizanoides Root Oil, Lavandin (Lavandula Hybrida) Oil, Citrus Aurantium Leaf Oil Paraguay, Rosmarinus officinalis (Rosemary) Leaf Oil

6. PHILLIP ADAM FRAGRANCE FREE SHAMPOO

No fragrance, No Parabens, No SLS (sulphate) but has CAPB

Ingredients: Purified Water (Aqua), Decyl Glucoside, Ammonium Cocollyssethionate, Cocamidopropyl Betaine, Apple Cider Vinegar, Caprylyhydroxamic Acid & Caprylyl Glycol & Glycerin, Lactic Acid, Hydrolyzed Pea Protein, Chamomilla recutita (Matriarca) Flower Extract, Melissa officinalis Leaf Extract (Lemon Balm), Urtica dioica (Nettle) Extract, Rosmarinus officinalis (Rosemary) Leaf Extract, Salvia officinalis (Sage).

7. GREEN CRICKET FRAGRANCE FREE SHAMPOO

No fragrance, No Parabens, No SLS (sulphate) but has CAPB

Ingredients: Aqua, cocamidopropylbetaine, cetyl betain, sodium methyl 2-sulfolaurate (and) disodium 2-sulfolaurate, vegetable glycerin, cocoglucoside, glyceryl oleate, aloe barbadensis (aloe) leaf juice, tocopherol acetate, glyceryl caprylate, glyceryl undecylenate
8. JASON FRAGRANCE FREE SHAMPOO

- No fragrance but has CAPB

- **Ingredients:** Aqua (Water), Aloe Barbadensis Leaf Juice (1), Cocamidopropyl Betaine, Sodium Lauryl Sulfoacetate, Chamomilla Recutita (Matricaria) Flower Extract, Salvia Officinalis (Sage) Leaf Extract, Ascophyllum Nodosum Extract, Guar Hydroxypropyltrimonium Chloride, Glycerin, Panthenol, Sodium Sulfate, Sodium Chloride, Citric Acid, Benzyl Alcohol, Potassium Sorbate, Sodium Benzoate

9. EARTH SCIENCE FRAGRANCE FREE SHAMPOO

- No fragrance but has CAPB

- **Ingredients:** Aqua (Water), Sodium Myreth Sulfate, Cocamidopropyl Betaine, Sodium Chloride, Chamomilla Recutita (Matricaria) Flower Extract, Simmondsia Chinensis (Jojoba) Seed Oil, Hydrolyzed Wheat Protein, Panthenol, Lactic Acid, Polyquaternium-7, Citric Acid, Hydroxypropyl Methylcellulose, Glycerin, Sodium Hydroxide, Potassium Sorbate, Sodium Hydroxymethylglycinate.

REFERENCE

QUESTION 7. A 49 year old female present with significant loss of both eyebrows. Blood tests include ferritin 35, TSH 3.1, and elevated FSH 26.6 IU/L. What is the most likely diagnosis?

A. Subclinical thyroiditis  
B. Alopecia areata  
C. Frontal fibrosing alopecia  
D. Polycystic ovarian syndrome

CORRECT ANSWER: C, Frontal Fibrosing Alopecia

COMMENTS AND DISCUSSION

The most likely cause of eyebrow loss in a 49 year old female with TSH in the normal range is frontal fibrosing alopecia. The elevated FSH signifies that the patient is likely peri-menopausal. Frontal fibrosing alopecia may begin with eyebrow loss for many women and can be challenging to diagnose at this stage because the eyebrow often appears relatively non-inflamed. In fact, many women with eyebrow FFA are diagnosed with alopecia. Injections of steroids into the eyebrow can prompt regrowth in some women with FFA as well as women with alopecia areata so this is not a helpful diagnostic test.

New onset bilateral eyebrow loss in a peri-menopausal or menopausal female must be viewed as frontal fibrosing alopecia until proven otherwise.

Diagnostic Pearl

New onset bilateral eyebrow loss in a peri-menopausal or post-menopausal female must be viewed as frontal fibrosing alopecia until proven otherwise.
A. **Subclinical thyroiditis (incorrect).** Thyroid disorders can give eyebrow loss. In this patient with TSH in the normal range, it is unlikely that thyroid disorders are a direct cause of the eyebrow loss. The presence of antibodies to thyroglobulin or thyroid peroxidase would indicate a thyroiditis that has the potential to progress to a hyperthyroid or hypothyroid state and in turn cause some loss of the eyebrow. Loss of the outer 1/3 of the eyebrow (Sign of Heritage) is sometimes seen in hypothyroid states.

B. **Alopecia areata (incorrect).** Alopecia areata is an important consideration for patients presenting with eyebrow loss. Frontal fibrosing alopecia is a far more likely diagnosis in a 49 year old female with bilateral symmetrical appearing loss of the brow.

C. **Frontal fibrosing alopecia (correct).** The most likely diagnosis of eyebrow loss in a 49 year old female is frontal fibrosing alopecia.

D. **Polycystic ovarian syndrome (incorrect).** Polycystic ovarian syndrome is not a cause of eyebrow loss
Question 8. A 31 year old male presents with almost complete loss of hair in both sideburns.

A. Diffuse unpatterned alopecia (DUPA)
B. Alopecia areata
C. Trichotillomania
D. Frontal fibrosing alopecia

CORRECT ANSWER: D, Frontal Fibrosing Alopecia

COMMENTS AND DISCUSSION

This case is given to illustrate is an important diagnostic pearl: namely that bilateral sideburn loss in a male is indicative of frontal fibrosing alopecia until proven otherwise. Although frontal fibrosing alopecia is far more common in women than men, it does occur in men and is easily missed given how infrequent it is – and how rarely most dermatologists see it. This simple diagnostic pearl allows the FFA to be picked up in the earliest possible stages.
A. Diffuse unpatterned alopecia (DUPA) (incorrect). DUPA is a form of androgenetic alopecia whereby the affected male develops thinning all over the scalp including the occipital scalp. Although sideburns could be thinned somewhat in a male with DUPA, this would occur later and it would not present as complete loss.

B. Alopecia areata (incorrect). Alopecia areata is an important consideration. In fact, most cases of male FFA are first misdiagnosed as alopecia areata. The striking symmetry that is typically present in males with FFA makes the diagnosis of alopecia areata unusual. Alopecia areata is generally more random rather than symmetrical.

C. Trichotillomania (incorrect). Trichotillomania has many different presentations. Bilateral sideburn loss is unusual, albeit not impossible, for patients with trichotillomania. Complete loss of hair in the area would be unusual and typically one side is favored more than another. Trichoscopy and patient history make allow differentiation in challenging cases.

D. Frontal fibrosing alopecia. (correct). Bilateral sideburn loss in males indicates a diagnosis of FFA until prove otherwise.

Reference
AlGaadi et al. Frontal fibrosing alopecia in a male presenting with sideburn loss 2015; 7: 72-3
QUESTION 9. Which of the following blood tests is most appropriate to order in a patient with alopecia areata?

A. 25 hydroxyvitamin D  
B. 1,25 hydroxyvitamin D  
C. Serum zinc  
D. AM cortisol

CORRECT ANSWER: A, 25 hydroxyvitamin D

COMMENTS AND DISCUSSION

Recent data has suggested that individuals with alopecia areata have a higher incidence of thyroid disease and vitamin D deficiency compared to individuals in the general population. From an evidence-based perspective, the blood tests that are the most cost effective to order in an adult patient with alopecia areata are TSH and 25 hydroxy-vitamin D.

In 2018, Lee and colleagues performed a meta-analysis of 14 studies. This included analysis of a total of 1255 alopecia areata subjects and 784 individuals without alopecia areata. The mean serum 25-hydroxyvitamin D level was significantly lower in AA subjects (-8.52 ng/dL; 95% confidential interval; -5.50 to -11.53). Individuals with alopecia areata were found to have a higher odds of vitamin D deficiency (odds ratio of 3.89; 2.02 to 7.49). Although some studies have suggested a relationship between low vitamin D and the severity of the alopecia areata, this particular meta-analysis did not find a clear correlation between serum 25-hydroxyvitamin D level and extent of hair loss in AA subjects. While vitamin D supplementation is recommended for individuals with alopecia areata found to have low vitamin D, we do not know if vitamin D supplementation actually supports or promotes hair growth.

A. 25 hydroxyvitamin D (correct answer). Vitamin D status is best assessed with serum measurement of 25 hydroxyvitamin D levels not 1,25 hydroxyvitamin D  
B. 1,25 hydroxyvitamin D (incorrect). Vitamin D status is best assessed with serum measurement of 25 hydroxyvitamin D levels not 1,25 hydroxyvitamin D levels.  
C. Serum zinc (incorrect). Zinc levels are appropriate to consider if history suggests a possible zinc deficiency. This might include individuals with poor dietary intake, or individuals with coexistent gastrointestinal disease or malabsorption syndromes.  
D. AM cortisol (incorrect). AM cortisol measurements would be warranted based on history.
References


Tsai TY and Huang YC. Vitamin D deficiency in patients with alopecia areata: a systematic review and meta-analysis. J Am Acad Dermatol 2018

QUESTION 10. Which of the following blood tests would be most appropriate to order in a 31 year old female with frontal fibrosing alopecia?

A. IGF-1  
B. Zinc  
C. FSH  
D. Celiac panel

CORRECT ANSWER: C, FSH

COMMENTS AND DISCUSSION

To date, there remains to evidence based practice guidelines about appropriate diagnostic work up or tests to order in the setting of frontal fibrosing alopecia. There is no good evidence that abnormal IGF-1 levels, zinc levels or celiac disease is more common in women with frontal fibrosing alopecia compared to controls. Certainly, blood tests for a variety of different parameters might be considered in situations where the history warrants such tests. For example, a patient with co-existent chronic diarrhea or poor dietary intake might also be screened for zinc levels. A patient with an iron deficiency anemia might be screen for celiac disease in the appropriate context.

The pathogenesis of frontal fibrosing alopecia remains to be fully elucidated. It is proposed to be an immune based disease, with many overlapping features of lichen planopilaris. In fact, it is currently classified as a subtype of lichen planopilaris.

Recent studies have suggested the hormonal dysregulation may be important to the pathogenesis of FFA. In 2017, Ranasinghe’s group at the Cleveland clinic found that women with FFA were more likely to have androgen deficiency compared to women with lichen planopilaris. In fact, Androgen excess was identified in approximately one-third of patients with LPP and androgen deficiency was identified in appropriately one-third of patients with FFA.

In 2014, Vano-Galvan and colleagues from Spain showed that young patients with FFA may also be at risk for early menopause. Their study was retrospective study looking back at some 355 patients seen in Spain. 14 % of women were reported to have premature menopause (early menopause). This is an important observation that it easily overlooked in a busy practice.
What is Premature menopause?

Premature menopause is defined as menopause occurring in women under 40 years of age. Overall, about 1% of women in the general population have premature menopause making the condition not really all that rare. A variety of genetic conditions, autoimmune conditions, infections, surgeries and medications (i.e. chemotherapies) can cause premature menopause. Without appropriate treatment, some of these women may be at increased risk of premature death, neurological diseases, psychosexual dysfunction, mood disorders, osteoporosis, ischemic heart disease and infertility.

Symptoms and signs of early menopause

The signs and symptoms of premature menopause are due in part to changing estrogen levels but other hormone levels are likely important as well. Symptoms of early menopause may include changes in menstrual cycles but may not. Symptoms may also include:

1. Hot flushes/night sweats
2. Vaginal dryness and painful intercourse
3. Urinary frequency, urgency and incontinence
4. Sexual dysfunction
5. Sleep problems
6. Headaches
7. Depression and anxiety and irritability
8. Joint pains
9. Poor concentration.
Screening for Early Menopause

Blood tests for estrogen (estradiol), FSH and LH, TSH, blood sugars, blood calcium levels are important tests to order in women who may be experiencing early menopause. Early menopause is associated with reductions in estradiol levels (E2 level <20 pg/ml) and a rise in FSH (FSH level >40 Miu/ml). Other screening tests may be considered depending on the results of estradiol and FSH including AMH (anti-Mullerian hormone) and ultrasound studies of the ovaries. If premature menopause is considered a bone mineral density should be considered to evaluate for possible osteopenia/osteoporosis. Referral to specialists including endocrinology and gynecology is important.

Medical Issues in Women with Early Menopause

Some of the medical issues that need to be reviewed with each patient have been outlined above and include hot flashes, night sweats, weight gain, sexual dysfunction, vaginal dryness, psychological issues like depression and anxiety, brain fog, irritability. The longer term consequences of osteoporosis, infertility, and cardiovascular disease/stroke are essential to review with appropriate medical teams.

A. IGF-1 (incorrect). There is no evidence for abnormal IGF-1 levels in individuals with FFA compared to individuals without FFA
B. Zinc. (incorrect). There is no evidence for abnormal zinc levels in individuals with FFA compared to individuals without FFA
C. FSH. (correct). Of all the options presented here, evaluation of FSH levels in a young woman age 31 with FFA has the most evidence. Although evidence based guidelines are lacking, tests for estradiol, FSH, TSH, CBC, 25 hydroxyvitamin D and an androgen panel should be considered.
D. Celiac panel (incorrect). There is no evidence for abnormal zinc levels in individuals with FFA compared to individuals without FFA

References


QUESTION 11. A 33 year old female with rapidly progressive hair loss is seen in clinic. Follicular miniaturization in the mid scalp is the main clinical findings. Labs show elevation of DHEAS by 4 fold above normal. With the exception of mild acne, the patient is otherwise healthy. Supplements include iron, vitamin D 2000 IU daily, biotin 10,000 mcg daily and zinc sulphate 50 mg daily. What is the most appropriate next step?

A. Evaluate 17 hydroxyprogesterone levels on day 3-5 of menstrual cycle.
B. Evaluate LH and FSH levels on day 3-5 of menstrual cycle
C. Arrange ultrasound of the abdomen
D. Stop the biotin and repeat blood tests

CORRECT ANSWER: D, stop the biotin and repeat the tests

COMMENTS AND DISCUSSION

Many supplements contain biotin at levels well above the recommended daily intake of 30 micrograms. Many supplements contain 2,500, 5,000 or even 10,000 micrograms of biotin. It is now recognized that high doses of biotin can interfere with some laboratory tests (specifically immunoassays using biotinylated antibodies). Depending on the lab test used, this may include tests for thyroid function and hormone tests (androgens, parathyroid hormone) as well as B12 assays.

Both falsely low and falsely high results are possible in users of biotin supplements. The concern is that some patients might undergo unnecessary testing or start unnecessary medications after being told their blood test results are abnormal. The FDA reported a case to the public of a person who died of a heart attack but whose troponins levels were falsely normal due to biotin intake.

The issue is therefore potentially quite serious. In November 2017, the US Food and Drug Administration recently issued a safety communication regarding biotin interference with laboratory tests.

A recent report in the Journal of the Endocrine Society reported a patient with abnormal thyroid results, as well as elevated cortisol and testosterone. These abnormal results prompted the patient to undergo numerous consultations and radiographic and laboratory tests. It was ultimately discovered in this patient that her abnormal results were due to the biotin supplement she was using. The patient was taking a biotin supplement at a dose of 5,000 micrograms per day regularly. Once she stopped biotin, her lab parameters returned to normal although TSH tests (thyroid testing) did take more than 2 weeks before any normalization was seen.
This report highlights the potential for patients using biotin to have false results. What is more concerning is the potential for such patients to undergo potentially invasive testing or start potentially harmful medications on account of these results.

Education as well as communication between health care teams, laboratories, and patients is vital to ensure patients stop biotin well ahead of any testing.

A. Evaluate 17 hydroxyprogesterone levels on day 3-5 of menstrual cycle. (incorrect). This screen for late onset congenital adrenal hyperplasia would be warranted if clinical history and repeat lab values once biotin is stopped remain abnormal.
B. Evaluate LH and FSH levels on day 3-5 of menstrual cycle (incorrect). This screen polycystic ovarian syndrome would be warranted if clinical history and repeat lab values once biotin is stopped remain abnormal.
C. Arrange ultrasound of the abdomen (incorrect). This test would be warranted if clinical history and repeat lab values once biotin is stopped remain abnormal. Additional imaging test may be important as well.
D. Stop the biotin and repeat blood tests. (correct). The labs can be repeated in 3 weeks.

Reference


4) Biotin-Related Interference in TSH, T4 and B12 Immunoassays Program: Abstracts - Orals, Poster Previews, and Posters Session: FRI 265-319-Thyroid Case Reports I (posters)

5) https://www.fda.gov/medicaldevices/safety/alertsandnotices/ucm586505.htm accessed Feb 1 2019
Question 13. A 53 year old female with a previous diagnosis of frontal fibrosing alopecia has noticed increasing roughness, bumpiness of her face. Which findings might be expected on biopsy of an affected area?

A. Dilation of sebaceous lobules  
B. Syringomatous hyperplasia  
C. Squamous syringometaplasia  
D. Mucinous degeneration

CORRECT ANSWER: A, Dilation of sebaceous lobules

COMMENTS AND DISCUSSION

Increased textural change on the face in a patient with frontal fibrosing alopecia suggests a diagnosis of so called “facial papules.” Although frontal fibrosing alopecia was first recognized as a condition that affects the frontal hairline it is now clear that the disease affects multiple areas of the body. Facial papules, of the development of small flesh colored bumps along with a roughening of skin are now recognized to be a part of the disease.

There remains some uncertainty as to what facial papules actually are – histologically speaking. Early studies by Dr Aline Donati in Brazil suggested that facial papules occurred due to an inflammatory attack by the immune system on tiny vellus hair follicles of the face. It was subsequently discovered that not all facial papules contain a vellus hair again raising issue as to how exactly these facial papules develop.
Pirmez and colleagues evaluated 3 mm punch biopsies from thirteen samples collected from 7 patients. Surprisingly, vellus hair follicle involvement was only seen in 2 of 13 (15.3%) of the biopsy specimens. 11 of the 13 specimens (85%) demonstrated prominent sebaceous glands and 10 of the 13 specimens (77%) showed dilated sebaceous ducts. Pinkus acid Orcein staining revealed reduction and fragmentation of the elastic fibers in 12 samples and, in 7 of these, this finding was observed in both the papillary and reticular dermis, particularly around sebaceous lobules. The conclusion of this study was that prominent sebaceous lobules with dilated sebaceous ducts associated with an abnormal elastic framework might in fact be the main explanation for the formation of facial papules in patients with FFA.

<table>
<thead>
<tr>
<th>Author</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Donati et al</td>
<td>• Inflammation of vellus hairs</td>
</tr>
<tr>
<td>Pirmez et al</td>
<td>• Only 2 of 13 (15.3%) of biopsies showed vellus hair involvement</td>
</tr>
<tr>
<td></td>
<td>• 11 of 13 specimens (85%) showed prominent sebaceous glands</td>
</tr>
<tr>
<td></td>
<td>• 10 of 13 specimens (77%) showed dilated sebaceous ducts.</td>
</tr>
<tr>
<td></td>
<td>• 12 of 13 samples showed reduction and fragmentation of elastic fibers</td>
</tr>
<tr>
<td></td>
<td>(Pinkus acid orcein staining)</td>
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</tbody>
</table>

FFA remains poorly understood. It has many similarities to classic lichen planopilaris and also many differences. In the hair loss community, we are programmed to review all the changes of FFA as somehow involving the hair follicles. As we come to understand the array of autoimmune conditions that can be associated with FFA and as we come to understand how other anatomical structures (such as the meibomian gland of the eyelashes) are involved, it is not unreasonable to postulate that pathology can occur in distinct structures such as the sebaceous gland and sebaceous lobules. Clearly more study is needed of facial papules in FFA, However, there responsiveness to treatment with isotretinoin does suggest that abnormalities in the sebaceous glands could in fact be contributory.

A. Dilation of sebaceous lobules (correct answer)
B. Syringomatous hyperplasia (incorrect)
C. Squamous syringometaplasia (incorrect)
D. Mucinous degeneration (incorrect)

Reference


A dermatologist is confused whether his patient might have lichen planopilaris or androgenetic alopecia …or even both. A biopsy is performed which shows perifollicular fibrosis and lymphocytic inflammation at the level of the isthmus. The T:V ratio is 3.2 to 1. What additional information from the biopsy would be helpful in making a final diagnosis?

A. No additional information is needed  
B. Density of sebaceous glands  
C. Perivascular inflammation  
D. Stem cell density

**CORRECT ANSWER: B, Density of sebaceous glands**

**COMMENTS AND DISCUSSION**

The finding of a terminal to vellus ratio of less than 4:1 is helpful here as this is typically suggestive of their being some degree of miniaturization happening and therefore a diagnosis of androgenetic alopecia.

<table>
<thead>
<tr>
<th>Hair Loss condition</th>
<th>T:V ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA</td>
<td>&lt; 4:1</td>
</tr>
<tr>
<td>CTE</td>
<td>&gt; 8:1</td>
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</tbody>
</table>

They key question then in this question then becomes … what information will be helpful to prove or disprove that lichen planopilaris also exists. An important point in this question is not to be lured into thinking that the finding on biopsy of “perifollicular fibrosis and lymphocytic inflammation at the level of the isthmus” equates with confirmation of a diagnosis of LPP. This is incorrect. These findings may be present in both LPP and androgenetic alopecia. It is the reduction in sebaceous glands and the precise effect of the inflammation (lichenoid change) that would point towards a diagnosis of lichen planopilaris.
It had long been thought that male and female patterned hair loss ('balding') is a relatively non-inflammatory process. The last decade has repeatedly shown that this is not the case and that inflammation is likely very much a part of the process and likely contributes in some way to the balding process itself. The current model of AGA suggests that ‘micro inflammation’ in AGA might trigger apoptosis and perifollicular fibrosis which in turn causes hairs to miniaturize and shed.

<table>
<thead>
<tr>
<th></th>
<th>AGA</th>
<th>LPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perifollicular fibrosis</td>
<td>May be Present</td>
<td>Typically Present</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Upper follicle</td>
<td>Upper follicle</td>
</tr>
<tr>
<td>Sebaceous glands</td>
<td>Preserved/prominent</td>
<td>Atrophic/reduced</td>
</tr>
<tr>
<td>Lichenoid change</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Elastic Verhoef van Giesen Staining</td>
<td>No follicular scars identified</td>
<td>Follicular scars identified</td>
</tr>
</tbody>
</table>

**Inflammation in AGA**

Inflammation is commonly seen in androgenetic alopecia and is likely part of the condition itself. Studies by Whiting showed that perifollicular inflammation was present in 40% of AGA biopsies. The inflammation present in AGA is different than the inflammation seen in the destructive scarring alopecias like lichen planopilaris. In 2000, Mahe used the term “microinflammation” to describe this types of inflammatory process.

Inflammation in AGA is mainly seen in the upper parts of the hair follicle. Inflammation is commonly found in both the isthmus and isthmus which are the upper portions of the hair follicle. Minor amounts of inflammation around hair follicles can be seen in the normal scalp as well in androgenetic alopecia. However, more marked degrees of inflammation are not normally seen in the scalp but can be a feature of androgenetic alopecia. In contrast to the inflammation in LPP, there is no lichenoid change in androgenetic alopecia and sebaceous glands are not reduced in AGA. Ramos in 2016 showed that inflammation is more common around miniaturizing hairs and this inflammation seems to be associated with a form of cell death known as apoptosis. In 1992, Jaworsky and colleagues showed that biopsies of males and females with androgenetic alopecia showed the presence of activated T-cell infiltrates about the lower portions of follicular infundibula. Inflammatory cells infiltrated the region of the
follicular bulge, the putative source of stem cells in cycling follicles. It was postulated that the progressive fibrosis of the perifollicular sheath might begin with T-cell infiltration of follicular stem cell epithelium and that the perifollicular fibrosis actually impairs hair growth.

Consequence of inflammation and fibrosis

The inflammation and fibrosis seen in androgenetic alopecia probably does matter. The inflammation likely triggers abnormalities in how hair cycles (i.e. telogen effluvium) and likely contributes to the progressive ‘miniaturization’ of hairs over time. Perifollicular inflammation in AGA appears to occur very early in the condition. In 2009, El-Domyati showed the perifollicular inflammation was present early the condition long before perifollicular fibrosis started to be seen. Over time, as perifollicular fibrosis became more commonly seen as perifollicular inflammation started to decrease. In other words, the two phenomena seemed to have an inverse correlation. Gonzalez showed in 2010 that perifollicular fibrosis was even a common finding in androgenetic alopecia occurring in teenagers.

Perifollicular inflammation and fibrous probably affect how hairs grow. In 1993, Whiting performed some classic studies that have shaped how we think about inflammation in AGA. He showed that patients with perifollicular inflammation and fibrosis have poorer responses to Minoxidil. Individuals with moderate or dense lymphocytic inflammation and perifollicular fibrosis may have poorer responses to Minoxidil.

What causes the perifollicular fibrosis anyways?

It’s not entirely clear what causes the perifollicular fibrosis to occur. In 2006, Yoo and colleagues proposed that TGF-beta (transforming growth factor beta) seemed to play a role. They showed that testosterone treatment increased the expression of type I procollagen at mRNA and protein level and this was associated with a rise in TGF-beta protein levels by 81.9 % in dermal fibroblasts. Conversely, pretreatment of finasteride inhibited the ability of testosterone to make pro collagen RNA and protein and decreased the expression of TGF-bet by 30 %. Interestingly, pretreatment of follicles with a TGF-beta antibody inhibited pro collagen expression leading the authors of the study to conclude that testosterone triggers TGF-beta expression and perifollicular fibrosis in AGA. They also postulate that one mechanisms of finasteride may be to reduce TGF-beta and therefore pro collagen expression.

Conclusion

Androgenetic alopecia is no longer viewed as a “non-inflammatory” condition. Inflammation is very much a part of AGA and this inflammation likely drives the development of perifollicular fibrosis and an inflammatory milieu that drives the apoptosis of dermal papilla cells and therefore the progression miniaturization of hair follicles. Distinction between AGA and LPP best comes from examining the density of sebaceous glands and the presence of lichenoid change. Special stains, including
elastic Verhoef van Gieson stains may help to identify true follicular scars that characterize scarring alopecia.

In 2018, Tan and colleagues from Northwestern University in Chicago used a special histological stain known as the elastic Verhoef van Gieson stain (EVG) to differentiate follicular streamers from follicular scars on horizontal scalp biopsy sections. They studied 64 scarring alopecias (25 lichen planopilaris, 29 central centrifugal cicatricial alopecias, and 10 discoid lupus erythematosus) and 53 non-cicatricial alopecias (34 androgenic alopecia, 8 telogen effluvium, and 11 alopecia areata), and EVG staining was performed on horizontal sections.

In follicular “streamers”, EVG highlighted an intact elastic network composed of delicate and thin elastic fibers circumferentially surrounding the angiofibrotic streamer. There was no elastic network attenuation, loss, clumping, thickening, or recoil. In contrast in the so called follicular “scars”, EVG demonstrated central attenuation and loss of the elastic network with peripheral clumping and recoil of elastic fibers.

These authors concluded that EVG staining can be helpful in cases where distinguishing between follicular streamers and scars is difficult. This stain may allow better discrimination between cicatricial and non-cicatricial alopecias.

A. No additional information is needed. (Incorrect). With the information provided, we do not have enough information to make the diagnosis.
B. Density of sebaceous glands (correct). This would be the most helpful information of these choices. A reduction in sebaceous glands density would support the diagnosis of a scarring alopecia. Of course, it would also be helpful to know about lichenoid change and whether true fibrous scars are present (if Elastic Verhoef van Gieson stains were done).
C. Perivascular inflammation. (incorrect). Perivascular inflammation does not assist us any further in making the diagnosis.
D. Stem cell density. (incorrect). In the present day, it is not easy to assay stem cell density. Loss of stem cell density might be in keeping with a diagnosis of scarring alopecia but this type of test/assay is not available.
REFERENCES


QUESTION 14. The histology of CCCA may differ from other scarring alopecias in which of the following ways

A. Inflammation is typically absent in CCCA  
B. Fat necrosis is more prevalent in CCCA  
C. Sebaceous glands are preserved in many cases of early-staged CCCA  
D. Premature desquamation of the inner root sheath is seen

CORRECT ANSWER: C, Sebaceous glands are preserved in many cases of early-staged CCCA

COMMENTS AND DISCUSSION

A key feature of scarring alopecias is thought to be the early destruction of sebaceous glands. In fact, in the prototypical primary scarring alopecia lichen planopilaris, atrophy or destruction of the sebaceous glands is thought to occur early in the course of the disease.

A new study by Dina and colleagues is causing us to rethink things a bit particularly when it comes to the view that sebaceous gland destruction is a key feature of scarring alopecia. Dina and colleagues studied 7 patients with CCCA and compared findings to 6 patients with LPP as well as for patients with non scarring alopecias. 5 of 6 LPP biopsies showed loss of sebaceous glands. However only 3 of 7 CCCA biopsies showed loss of sebaceuous glands. Not unexpectedly, all non scarring alopecia biopsies showed preservation of sebaceous glands.

This new information suggests that preservation of the sebaceous glands may be more a part of the histology of CCCA than previously realized. It may be time to rethink the sebaceous gland again and what it exactly means in all these primary scarring alopecias.
A. Inflammation is typically absent in CCCA (incorrect). CCCA is a lymphocytic scarring alopecia. While inflammation in CCCA may be less at times than seen in typical cases of LPP, inflammation is very much a part of CCCA.

B. Fat necrosis is more prevalent in CCCA. (incorrect). This is not a feature of CCCA.

C. Sebaceous glands are preserved in many cases of early-staged CCCA. (correct).

D. Premature desquamation of the inner root sheath is pathognomonic of CCCA. (incorrect). Premature desquamation of the inner root sheath is not pathognomonic of CCCA. It is a typical feature of CCCA but can be seen in other scarring alopecias. In CCCA, it was first noted that there is an unusual separation of the IRS from the ORS deep down in the skin. This is referred to as Premature desquamation of the inner root sheath (PDIRS). For several years it was thought that PDIRS was a pathognomonic and distinctive feature of CCCA until data emerged that it is also seen in other types of scarring and non-scarring alopecia.

Tan and colleagues chose to re-investigate this concept of the PDIRS in CCCA. Although the authors were aware that PDIRS was a feature of many scarring alopecia, they specifically wanted to determine whether PDIRS in “non-inflamed” follicles could be used as a specific marker of CCCA. To do so, they performed retrospective study of 501 histologically unambiguous cases of alopecia (111 of CCCA, 102 of lichen planopilaris, 62 of discoid lupus erythematosus, 16 of acne keloidalis nuchae, 27 of folliculitis decalvans, 80 of androgenetic alopecia, 97 of alopecia areata, and 6 of psoriatic alopecia).

As expected they found that PDIRS was identified in all alopecia subtypes evaluated. PDIRS was identified in lichen planopilaris, discoid lupus erythematosus, acne keloidalis nuchae, and alopecia areata, 100% of cases were in inflamed follicles. PDIRS in non-inflamed follicles occurred in 73% (81/111) of CCCA. It also occurred in the scarring alopecia folliculitis decalvans, but this was uncommon being seen in 11% (3 of 27 patients). PDIRS around non-inflamed follicles was also uncommon in most non scarring alopecia being seen in 33% (2/6) of psoriatic alopecia, and 1% (1/97) of androgenetic alopecia. Overall, the presence of PDIRS in at least one non-inflamed hair follicle correlated with a diagnosis of CCCA with a sensitivity of 73% and a specificity of 98% (P-value <0.0001).

Reference

Question 15. A 55 year old female has chronic shedding. A biopsy was obtained and a terminal to vellus ratio of 8:1 is noted. The patient has a variety of scalp symptoms despite the fact that the scalp surprisingly looks completely normal during examination. Which of the following treatments are most likely to help this patient’s shedding?

A. Finasteride  
B. Oral Minoxidil  
C. Hydroxychloroquine  
D. Gabapentin

CORRECT ANSWER: B Oral Minoxidil

COMMENTS AND DISCUSSION

This is a very typical presentation of patients with true chronic idiopathic telogen effluvium (CTE). Patients with CTE present with fluctuating amounts of shedding and in the case of isolated CTE – the scalp looks surprisingly normal. Biopsy of the scalp fails to show miniaturization in the case a patient with just the diagnosis of CTE. The T:V ratio in patients with CTE is often above 8:1 although this may be challenging to capture in a single biopsy. Several biopsies may be needed.

<table>
<thead>
<tr>
<th></th>
<th>T:V ratio</th>
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<tbody>
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<tr>
<td>CTE</td>
<td>&gt; 8:1</td>
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</table>

Patients with CTE may present with a range of scalp symptoms including itching, burning, pins and needles and trichodynia.

Treatment for CTE is challenging. Agents such as topical Minoxidil, oral Minoxidil, low level laser, hair vitamins/hair supplements, biotin are all considered but good evidence based studies are lacking.

In 2017, Dr Rod Sinclair and colleague Dr Perera set out to examine the benefits of oral minoxidil in the treatment of CTE. In total, 36 female patients (mean age 46.9) with CTE were treated with oral minoxidil (range, 0.25-2.5 mg) daily for 6 months. Oral minoxidil was found to reduce shedding. 5 of the 36 women who noted trichodynia (scalp pain) at baseline had improvement at 3 months. Interestingly, all 36 women completed the 12 months study indicating side effects were likely manageable for them.
Mean blood pressure change was only 0.5 mmHg systolic and 2.1 mmHg diastolic. 2 patients had dizziness that improved over time even with continuation of treatment. 13 (36 %) women developed increased hair on the face. 1 patient developed swelling of the ankles.

This was an interesting study. The treatment of CTE tends to be frustrating for doctors and patients alike. Some patients respond to standard treatments but certainly not all. This study offers hope that oral minoxidil could also be added to the list of treatments for this frustrating shedding condition. Oral minoxidil does appear safe and we have been using it in clinic for some time. The most common side effects are the increased hair on the face (especially upper lip) and body that some patients get. Dizziness, headaches, hives, ankle swelling are among the other side effects.

The most common side effect in practice is increased hair on the upper lip in 25-35 % of women. Other less common side effects are typically headaches, ankle swelling, hives. Surprisingly, shedding does not tend to be very common when starting

REFERENCE

Question 16. This machine provides a method for performing

A. Follicular unit extraction (FUE) surgery
B. Follicular unit strip surgery (FUSS/FUT)
C. Stem cell harvesting
D. Platelet rich plasma extractions

CORRECT ANSWER: A Follicular unit extraction (FUE) surgery

COMMENTS AND DISCUSSION

The photo show the FDA approved ARTAS robotic hair restoration device. It was approved by the FDA in 2011 for treating brown and black hair males. It removes hair by the follicular unit extraction technique. The occipital scalp (donor area) is first shaved and the robot arm is place over the shaved area. Using a 1 mm punch, follicles are removed from the area using laser assistance. The punch is a circular device which removes the grafts from the skin. There are two aspects to the punch - one inner sharp punch and one outer dull punch. The first inner sharp punch scores the skin to a depth of about 1/16th of an inch. The is followed by the outer dull punch with extracts the grafts.
Follicular Unit Extraction (Occipital Scalp)
Question 17. A 52 year old female presents with an 18 months history of hair thinning. Her history includes breast cancer at age 50 treated with multiple chemotherapeutic agents including docitaxel. Her hair never really grew back fully after chemotherapy and she is worried about the effects of her current letrozole pills because her hair continues to thin. Which treatment is most likely to provide benefit for this patient’s hair?

A. Finasteride  
B. Scalp cooling  
C. Minoxidil  
D. Platelet rich plasma  

CORRECT ANSWER: C, Minoxidil  

COMMENTS AND DISCUSSION  

This is an example of a patient with hair thinning possibly from two causes:  
   a) permanent chemotherapy induced alopecia from docitaxel  
   b) endocrine therapy induced alopecia from the aromatase inhibitor letrozole.  

Minoxidil is a good starting point for both these types of hair loss. Every year about 650,000 patients undergo chemotherapy in the United States. Hair loss is a common side effect of chemotherapy and occurs in about 65 % of patients who receive chemotherapy. There are two main types of hair loss that can occur in patients undergoing chemotherapy. The first is hair loss that happens within weeks of starting the chemotherapy and then lasts several months before growing back. This is known as temporary chemotherapy induced alopecia ("TCIA"). The second type is uncommon and occurs when patients fail to regrowth their hair back to the level it was before undergoing chemotherapy. If hair has not grown back after chemotherapy by the 6 month after chemotherapy, we call this permanent chemotherapy induced alopecia (PCIA) and it is sometimes also called Chemotherapy Induced Permanent Alopecia (CIPAL). In this particular case above, the failure of the patient’s hair to grow back after chemotherapy suggested PCIA is one of her diagnoses. 

TCIA  
Temporary Chemotherapy Induced Alopecia  

PCIA  
Permanent Chemotherapy Induced Alopecia  

ETIA  
Endocrine Therapy Induced Alopecia
Permanent Chemotherapy Induced Alopecia (PCIA)

The failure of the hair to grow back fully 6 months post chemotherapy raises concerns about a phenomenon known as permanent chemotherapy induced alopecia (PCIA). In recent years a number of studies have highlighted the possibility of PCIA in women with breast cancer treated with various chemotherapeutic agents, especially drugs known as “taxanes”. Docetaxel and paclitaxel are part of this group of drugs. The exact mechanisms are unclear although injury to the bulb as well as follicular stem cells are thought to be relevant. Adjuvant anti-estrogen hormonal therapy may be an important cofactor in many women with PCIA. A similar PCIA presentation has been reported in patients undergoing bone marrow transplantation. The scalp is predominantly affected in women with PCIA although a minority may have eyebrow, eyelash and body hair loss as well. We don't really know yet how to best treat PCIA. The most common treatments described in the medical literature are oral and topical minoxidil. Both seem to provide benefit to at least a proportion of patients.

Endocrine Therapy Induced Alopecia (ETIA)

Tamoxifen and aromatase inhibitors are common medications used to block the effects of estrogen in patients with breast cancer. It is now understood that hair loss can be a potential side effect of these medications. The best means to treat the hair loss remains unclear.

Trueb and colleagues performed a retrospective cohort study of 112 patients with breast cancer who had experienced hair loss with these drugs. Hair loss was attributed to aromatase inhibitors in 75 patients (67%) and tamoxifen in 37 (33%). 46 of the 112 patients (41%) underwent treatment with minoxidil. 37 of the 46 patients (80%) had moderate or significant improvement in their hair loss with Minoxidil therapy.

A. Finasteride (incorrect). While the features of PCIA and ETIA are similar to androgenetic alopecia, anti-androgens are not known to benefit. Use of antiandrogens such as finasteride in women with a previous diagnosis of breast cancer relative contraindication (despite the fact that there is no good evidence these medications cause cancer)

B. Scalp cooling. (incorrect). Scalp cooling is a method to reduce the chances of hair loss in a patient undergoing chemotherapy. It is not a method to reduce hair loss in patients who have already received chemotherapy.

C. Minoxidil (correct answer). Topical and oral Minoxidil are options to consider in patients with hair loss after chemotherapy.

D. Platelet rich plasma. (incorrect). There is no good evidence to date that would support that use of PRP in patients who have experienced hair loss from chemotherapy.
REFERENCES


Rugo HS. Real-world use of scalp cooling to reduce chemotherapy-related hair loss. Clin Adv Hematol Oncol. 2017

Question 18. Which of the following patients is least likely to experience some degree of improvement in hair density with treatment?

A. A 25 year old female with alopecia universalis since age 4 who is now starting tofacitinib
B. A 41 year old male with recent onset dissecting cellulitis now starting isotretinoin and antibiotics
C. A 33 year old female with recent onset discoid lupus now starting triamcinolone acetonide injections, topical steroids and hydroxychloroquine
D. A 49 year old female with newly diagnosed frontal fibrosing alopecia now starting finasteride

CORRECT ANSWER: A A 25 year old female with alopecia universalis since age 4 who is now starting tofacitinib

COMMENTS AND DISCUSSION

This is an important question because it emphasizes two points. First, some non-scarring alopecias are more challenging to regrow hair than some scarring alopecias. Second, the early and aggressive treatment of some types of scarring alopecias may lead to some amount of regrowth. This includes discoid lupus, dissecting cellulitis. Recently, with the realization of the potential benefits of the 5 alpha reductase inhibitors (finasteride and dutasteride) for treating frontal fibrosing alopecia, FFA is also on the list of scarring alopecias that may regrowth to some degree with treatment.

In 2014, Vano-Galvan and colleagues reported the effects of antiandrogens finasteride and dutasteride in 111 patients. In their study, improvement was seen in in 52 patients (47%) and stabilization was seen in in 59 patients (53%).

References

Question 19. A 53 year old female with a previous diagnosis of frontal fibrosing alopecia has noticed increasing roughness, bumpiness of her facial skin. Which treatment is likely to be most effective?

A. Topical hydrocortisone valerate
B. Topical pimecrolimus
C. Oral finasteride 2.5 mg
D. Oral isotretinoin

**CORRECT ANSWER: D, Oral isotretinoin**

**COMMENTS AND DISCUSSION**

It is now recognized that facial papules are part of the clinical presentation of frontal fibrosing alopecia. In fact, they may be an important feature to identify as they may portend poorer prognosis.

The optimal treatment for facial papules has not been clear. In the last 2 years, and increasing number of reports have suggested that low dose isotretinoin may be an important consideration. In 2018, Flores-Terry and colleagues reported 2 patients in 2018 who were treated with low dose isotretinoin with benefit. Interestingly both had used hydroxychloroquine (i.e. Plaquenil) in the past without benefit. This study by Flores-Terry et al is very much in keeping with the 2017 study by Pedrosa AF and colleagues. They found that facial papules were found in 62 of 108 patients with FFA. When 10 mg isotretinoin every other day (3 times weekly) was added to other therapies like finasteride or spironolactone, an improvement in facial roughness was seen in 2-4 months.

A. **Topical hydrocortisone valerate (incorrect).** Based on current evidence, this is not likely to be the most effective treatment.
B. **Topical pimecrolimus (incorrect).** Based on current evidence, this is not likely to be the most effective treatment.
C. **Oral finasteride 2.5 mg. (incorrect).** Based on current evidence, this is not likely to be the most effective treatment.
D. **Oral isotretinoin (correct).** Low dose isotretinoin appears to be among the most effective options for treating the facial papules in patients with frontal fibrosing alopecia.


QUESTION 20. A 42 year old female has recently developed 6 coin shaped patches of alopecia areata. Her past medical history includes psoriasis and current medications include adalimumab which was started 8 months ago. Which of the following diagnostic and treatment options would be appropriate to discuss with the patient?

A. Obtain blood tests TSH and 25 hydroxy-vitamin D  
B. Consider starting steroid injections  
C. Consider stopping adalimumab  
D. All of the above  

CORRECT ANSWER: D, All of the above  

COMMENTS AND DISCUSSION  
All of these are appropriate steps to take in a patient with alopecia areata who has also recently been started on a TNF inhibitor. Blood tests are appropriate as part of the general work up and the precise tests to order are typically dictated by the history. CBC, TSH, ferritin, vitamin D are common labs to order. B12, ANA, ESR, hormone levels, zinc, syphilis screening may also be appropriate on a case by case basis.  

In a patient with 6 coin shaped patches, starting steroid injections with 2.5 to 5 mg per mL triamcinolone acetonide may be very appropriate. The addition of Minoxidil and a topical steroid can be considered for home use as well. Steroid injections can be repeated again in 4-6 weeks, if needed.  

Recent research in the past decade has shown the TNF inhibitors can, in rare cases, contribute to the development of alopecia areata as well as other types of hair loss as well (i.e. psoriatic alopecia and scarring alopecias). Alopecia areata has been reported with all three anti-TNF agents including adalimumab, etanercept and infliximab. To date, the most common TNF-inhibitor implicated is adalimumab followed by infliximab and etanercept.  

In affected patients, hair loss can occurs with a matter of months to many years after the TNF agent is started. Of all the reports in the medical literature to date, onset in affected patients may occur fastest with adalimumab (6.8 months average) compared to over 1 year with the other 2 agents. The degree of hair loss varies greatly from patchy type AA to alopecia totalis and universalis.
Optimal treatment for TNF inhibitor induced AA is not clear. Some patients have improved their hair by stopping the TNF inhibitor although a smaller proportion may improve even with continued use of the TNF inhibitor or switching the type of TNF inhibitor used. The option with the highest chance of success in terms of stopping hair loss and regrowing hair appears to be stopping the anti-TNF agent.

Reference
Craddock LN et al. TNF inhibitor induced alopecia: an unusual form of psoriasiform alopecia that breaks the Renbok mold. Dermatol Online J. 2017 Mar 15;23(3).

Question 21. Use of low level laser therapy (LLLT) might be considered in which of the following situations?

A. 25 year old female with androgenetic alopecia  
B. 45 year old female with lichen planopilaris  
C. 51 year female having just completed chemotherapy last  
D. All of the above

CORRECT ANSWER: D, All of the above

COMMENTS AND DISCUSSION

Low level laser devices are FDA cleared for treatment of androgenetic alopecia. A number of recent systematic reviews and meta-analyses of randomized trials support the efficacy of these devices over sham type devices. Emerging evidence suggests that low level laser type devices may also have benefit in the management of scarring alopecias such as lichen planopilaris as well as in prompting more rapid regrowth in patients receiving chemotherapy.

In a 2017 study, Fonda-Pascual and colleagues from Spain set out to examine the benefits of LLLT in patients with lichen planopilaris. The study itself was designed as a 6 month prospective interventional study and the goal was to follow the activity of the disease before and after treatment using the so called lichen planopilaris activity index (LPPAI). Videodermoscopy was used to follow 5 specific areas for perifollicular redness and perifollicular scale as well as to follow hair thickness. The study itself was small with 8 patients (3 males 5 females). Patient had LPP for an average of 3-4 years (mean 44.25 months). A laser helmet based device with 246 LEDs was used (each with a wavelength of 630 nm and fluency of 4 J/cm2). Interestingly, all patients had a reduction in symptoms, redness and scaling and there was a decrease in the LPPAI after 6 months. An increase in hair thickness was also measured.

The use of low level laser is increasingly studied in oncology where recent studies in both mice and humans have shown that low level laser may accelerate the speed of the regrowth that happens after chemotherapy.
REFERENCE


Question 22. A 27 year old female with lichen planopilaris recently started hydroxychloroquine 400 mg daily last week. The patient is healthy and her current weight is 112 pounds. She will be seen by the eye doctor tomorrow. Assuming the eye examination is normal, current recommendations would support which of the following outcomes?

A. Continue at 400 mg daily and see back in 6 months  
B. Continue at 400 mg daily and see back in 5 years  
C. Reduce to 200 mg daily and see back in 5 years  
D. Reduce to 200 mg and see back in 6 months

CORRECT ANSWER: C, Reduce to 200 mg and see back in 5 years

COMMENTS AND DISCUSSION

Hydroxychloroquine is an oral medication used in a variety of autoimmune conditions including lichen planopilaris. A number of eye-related side effects are possible ranging from vision changes to double vision to asymptomatic changes in various parts of the eye.

The Risk of Retinopathy with Hydroxychloroquine

"Retinopathy" is one of the more worrisome side effects of Hydroxychloroquine. At appropriate doses, studies show that the risk appears to be about 1% of patients at 5 years of use and 2% at 10 years. After 20 years, the risk may rise to 20%. Once the retinal toxicity from hydroxychloroquine occurs, it is believed that the changes in the retina are permanent. Furthermore, the disease can even progress even if hydroxychloroquine is stopped.

<table>
<thead>
<tr>
<th>Years of Treatment</th>
<th>Risk of Retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years</td>
<td>1 %</td>
</tr>
<tr>
<td>10 years</td>
<td>2 %</td>
</tr>
<tr>
<td>20 years</td>
<td>20 %</td>
</tr>
</tbody>
</table>
Risk Factors for Retinal Toxicity

Retinal damage can occur in anyone. However, the risk may be increased if the following risk factors are present:

- Longer Duration of use (cumulative dose)
- Renal or hepatic functional impairment.
- Compromised kidney and/or liver function can lead to increased accumulation of hydroxychloroquine in the tissues.
- Age over 60 years.
- Preexisting retinal disease
- Concurrent tamoxifen therapy

What dose should I take?

It's clear that taking the appropriate dose reduces (but does not eliminate) the chance of side effects. The optimal dose is 6.5 mg for every kg of lean body weight (not simply what the patient weighs). "Lean body weight" is essentially the patient's expected weight for their height and gender - it does not include the "extra" weight that some might carry. Instead of calculating lean body weight, many clinicians now advocate simply using the patient's true body weight and multiplying by 5 (instead of 6.5).
Table 1: TYPICAL HYDROXYCHLOROQUINE DOSING

<table>
<thead>
<tr>
<th>WEIGHT OF PATIENT (LBS)</th>
<th>DOSE I TYPICALLY USE</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>200 mg daily every day of the week</td>
</tr>
<tr>
<td>110</td>
<td>200 mg daily every day of the week</td>
</tr>
<tr>
<td>120</td>
<td>200 mg daily Monday to Friday; 400 mg on weekends</td>
</tr>
<tr>
<td>130</td>
<td>Alternate 200 mg and 400 mg</td>
</tr>
<tr>
<td>140</td>
<td>Alternate 200 mg and 400 mg</td>
</tr>
<tr>
<td>150</td>
<td>400 mg daily Monday to Friday; 200 mg on weekends</td>
</tr>
<tr>
<td>160</td>
<td>400 mg daily Monday to Friday; 200 mg on weekends</td>
</tr>
<tr>
<td>170</td>
<td>400 mg daily Monday to Friday; 200 mg on weekends</td>
</tr>
<tr>
<td>180 and above</td>
<td>400 mg daily</td>
</tr>
</tbody>
</table>

For a patient weighing 112 pounds, the dose would be 200 mg daily.

Overall, the risk of eye related toxicity is low in the first 5-10 years of hydroxychloroquine use provided the dosing is respected. Recent studies including those below have helped to better define the real magnitude of retinopathy risk and has encouraged changes in screening guidelines. These guidelines now include an initial examination but dedicated yearly screening to begin only after 5 years in otherwise healthy individuals deemed at low risk for eye problems.

AMERICAN ACADEMY OF OPHTHALMOLOGY SCREENING SCHEDULE

A baseline fundus examination should be performed to rule out preexisting maculopathy. Begin annual screening after 5 years for patients on acceptable doses and without major risk factors.
A. Continue at 400 mg daily and see back in 6 months (incorrect). This dose is too high for the patient. A dose of 5 mg/kg means the maximum daily dose is 254 mg. In a healthy patient with no risk factors, re-evaluation at the 5 year mark would be acceptable.

B. Continue at 400 mg daily and see back in 5 years. (incorrect). This dose is too high for the patient. A dose of 5 mg/kg means the maximum daily dose is 254 mg.

C. Reduce to 200 mg daily and see back in 5 years. (correct). This is the best answer. With a weight of 112 pounds, and no risk factors for eye disease, the patient can be started on 200 mg daily. Following an initial evaluation, new guidelines would support re-evaluation at year 5.

D. Reduce to 200 mg and see back in 6 months. (incorrect). In some ways, of course, this answer is also correct because re-evaluation at the 6-12 months mark will continue to be a common protocol for many physicians. However, the current research would support less frequent eye evaluations during the initial period.

REFERENCE


AAO Quality of Care Secretariat. Hoskins Centre for Quality Eye Care. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy 2016. March 2016
Question 23. A 5 year old with low iron is started on iron supplementation with a liquid iron syrup. Her parents are using a total of 100 mg of elemental iron. Her current weight is 40 pounds (18 kg). 8 weeks into treatment the child has stained teeth. What is the appropriate next step?

A. Decrease the dose to a more age appropriate level  
B. Take with milk  
C. Brush the teeth with baking soda  
D. All of the above

CORRECT ANSWER: C Brush with baking soda

A conversation with parents regarding iron never begins with a conversation about iron. The conversation must begin with a broader overview of the child’s growth and development. Consideration is needed as to whether there could be other nutrition deficiencies and whether there are other health issues present. For some children, genetic conditions also affect the ability to make blood cells and store iron (i.e. the thalassemias). In fact, a wide variety of issues can contribute to low iron in children! A full review is needed.

Children with iron deficiency should be evaluated by the pediatrician especially when there is an anemia (hemoglobin levels less than the cut of level). The pediatrician can decide whether further blood tests are needed. This may include screening tests for hemoglobinopathies as well as screening tests for other deficiencies that might be present together with the iron deficiencies. Screening for celiac disease might also be considered in some children with low hemoglobin and low ferritin levels. In addition, the pediatrician can perform and examination and get more information about the child’s dietary practices.

For children with normal hemoglobin and slightly low ferritin levels, one can begin by reviewing dietary means of increasing iron rich foods in the diet. This includes red meats, poultry, fish, shellfish, lentils, beans. I always encourage parents to go slow with their approach to increasing iron and start first with reviewing the diet. Dietary means are generally the best to start with and encourage life long healthy eating in the child. If dietary means are sufficient and low ferritin levels are still present, (or if it’s just not possible to raise ferritin levels with dietary changes), short term iron supplementation can be considered.

The appropriate dose of iron in a child is 5-6 mg per kg of elemental iron.
How should iron be taken?

Iron can be taken with water or fruit juice or tomato juice as this really helps absorption. It should not be taken with milk. The iron can be taken 1 hour before eating or 2 hours after. Taking on an empty stomach really helps with absorption. If children develop an upset stomach, it can be taken 20 minutes after eating or even with food.

Staining of the teeth is a possible side effect of iron as is constipation (and rarely looser stools too). I always advise parents to go slow and start with half the dose for 1 week to make sure the child will tolerate it well. To prevent or at least reduce the chances of staining of the teeth, the liquid can be taken with a straw. Brushing the teeth twice daily and using baking soda to remove stains while brushing can also help a lot.
Iron Supplements: How long are they taken?

Iron supplements should always be prescribed with a definitive start and stopping date. For children, I recommend checking ferritin (and hemoglobin) levels again in three months. If levels have risen to the appropriate level iron can be reduced or even stopped. Repeat monitoring may then be appropriate again 6 months to 12 months down the road to ensure that levels have not plummeted. Chronic iron supplementation without a stop date (or recheck date) is not advisable for children.
Question 24. A 51 year old woman on finasteride 2.5 mg presents to clinic with concerns about the medications she is using. She had previously used Spironolactone 100 mg daily for several years but stopped recently due to hypotension. She was told by another physician that these medications cause breast cancer. She has no personal or history of breast cancer.

A. Studies in women suggest that finasteride and spironolactone increase the risk of breast cancer
B. Studies in women suggest that finasteride increases the risk of breast cancer but spironolactone does not
C. Studies in women suggest that neither finasteride nor spironolactone increase the risk of breast cancer.
D. Studies in women have not been done with finasteride but studies with spironolactone would suggest there is no increased risk

CORRECT ANSWER: D, Studies in women have not been done with finasteride but studies with spironolactone would suggest there is no increased risk

There are no current practice guidelines anywhere in the world to guide decisions on starting anti-androgen therapy in a patient with a family history of breast cancer. Some physicians are of the opinion not to use anti-androgens – i.e. that anti-androgens are relatively contraindicated in women who have a first-degree relative with breast cancer. *To date, there is no strong evidence that use of anti-androgens modify the risk of breast cancer in women at “low risk” for the disease. It is less clear if anti-androgens modify the risk of breast cancer in women at high risk for the disease.* I generally advise that patients and physicians review their risk for breast cancer using various helpful online risk calculators such as the NIH risk calculator.

https://bcrisktool.cancer.gov
Risk of breast cancer with anti-androgen therapy

To date, there is no good evidence to support the notion that use of oral anti-androgens such as finasteride or spironolactone are associated with an increased risk of breast cancer in women either in the general population or in women at increased risk of breast cancer. For finasteride, studies looking closer at breast cancer risk in women have never been done and we rely entirely on studies in males at low risk. For women, only a few studies have looked at breast cancer risks in spironolactone users. These studies have not suggested an increased risk of cancer in spironolactone users who are at low risk for breast cancer.

We do not have data on the risk of breast cancer in users of anti-androgens at highest risk

I will first address what is known at present about the risk of breast cancer from finasteride and then from spironolactone and then address how a patient may come to get a better estimate of risk. References for all the studies discussed are provided at the end.

For finasteride-related risk, the best means we have in the present day of addressing this question is by looking at the risk of breast cancer in men using finasteride and extrapolating the data the best we can to estimate the potential risk in female users. We do not have studies in women. Male breast cancer is a rare condition with a lifetime risk of 0.1 %. In men, its behavior is similar to breast carcinoma in postmenopausal women.

There have been case reports and clinical trial results that suggested that treatment with 5ARIs may be associated with male breast cancer. Most studies to date however, suggest that it is not. All data needs to be taken into context with all available data to date. It should be noted that a warning label has been placed on finasteride packaging in many countries until this issue is further evaluated. An evidence review by the United Kingdom’s (UK) national drug agency resulted in a finasteride drug warning label for breast cancer in the UK and Canada and initiation of an FDA safety probe for all 5ARIs in 2010.

It is impossible to ascertain risk of cancer from clinical trials alone. This is become such typical clinical trials are neither large enough nor have long enough follow-up to identify male breast cancer cases in men who use finasteride. The best type of studies we have at present are observational studies where men with breast cancer are compared to men without breast cancer. Such “case-control studies” are an invaluable tool to assess this important question. Ii will review many such case control studies below.
2016-2018 PUBLISHED STUDIES ON FINASTERIDE AND BREAST CANCER IN MEN

Meijer and colleagues recently assessed the possible relationship between finasteride and breast cancer by combining nationwide registers in 4 countries (Denmark, Finland, Norway, and Sweden) to assess the potential association between finasteride and male breast cancer. A cohort of all males with dispensed finasteride (1,365,088 person years) was followed up for up to 15 years for breast cancer, and compared to a cohort of males not receiving finasteride. An increased risk of male breast cancer was found among finasteride users (IRR = 1.44, 95% confidence interval [95% CI] = 1.11-1.88) compared to nonusers. The analyses suggested possible ascertainment bias and did not support a clear relationship between dispensed finasteride and male breast cancer.

Hagberg et al conducted a cohort study with nested case-control analyses using the UK Clinical Practice Research Datalink. 5ARI users did not have an increased risk of breast cancer compared to unexposed men (OR=1.52, 95% CI 0.61–3.80).

2013-2015 PUBLISHED STUDIES ON FINASTERIDE AND BREAST CANCER IN MEN

In 2014, Duijnhoven and colleagues in the Netherlands performed a case-control study with data from the United Kingdom Clinical Practice Research Datalink database among all men aged 45 years and older. Cases of men diagnosed with breast cancer were matched to up 10 controls. There were 398 cases were identified and matched to 3,930 controls. The “ever use” of 5-ARIs (finasteride and Dutasteride) was associated with an adjusted odds ratio for breast cancer of 1.08 (95% CI 0.62-1.87) compared to non-users. Increasing cumulative duration of treatment showed no increasing risks. The conclusion here in Duijnhoven’s study was that there was no evidence of an association between short- or long-term treatment with 5-ARIs and the risk for breast cancer in older men.

In 2013, Bird and colleagues in the United States published a cased control study of men age 40 to 85 years old. Here there were 339 breast cancer cases matched to 6,780 controls. There were no statistically significant associations observed between 5α-reductase inhibitors and breast cancer regardless of exposure assessment. Their conclusion was that the lack of an association in our study suggests that the development of breast cancer should not influence the prescribing of 5α-reductase inhibitor therapy.
2003-2012 Published Studies on Finasteride and Breast Cancer in Men

In the 2003 PCPT study, Thompson and colleagues published data on 18,882 men aged 55 years or older who were randomized to treatment with 5 mg/day finasteride (n = 9,423) or placebo (n = 9,459) for 7 years. One case of breast cancer was reported as an adverse experience in each treatment group during the study. **In this very large long-term study, an increased incidence of breast cancer in the finasteride group compared to placebo was not observed.**

The main study that drew attention to a potential relationship between finasteride and breast cancer was a 2003 study by McConnell. In this study, 3,047 patients were randomized to a double-blind, multi-center, placebo-controlled clinical trial for 4-6 years. The 4 different patient groups were administered different drugs: placebo; 8 mg doxazosin; 5 mg finasteride and a combination of 8 mg doxazosin and 5 mg finasteride. Three cases of breast cancer occurred in the finasteride-treated group and 1 case of breast cancer occurred in the combination group. No predisposing factors were identified. Duration of treatment ranged from 1.8 years to 5 years. The occurrence of 4 cases of breast cancer in 3,047 patients was considered high considering the normal incidence in the general population of 1 case in 100,000 man-years. **Treatment with finasteride appeared in this study to confer 200-fold risk for breast cancer in comparison to patients not receiving the drug.**

1996-2002 Published Studies on Finasteride and Breast Cancer in Men

In 1996, Prescription Event Monitoring (PEM) Study was published. This study was conducted by Drug Safety Research Unit (DSRU) and involved a total of 14,772 patients (mostly male) under observation of General Practitioners from 1992–1994. There were 2 reported breast carcinomas. For one of the events, the time to onset from commencement of finasteride treatment was recorded as 5 months, the other was unknown. **The PEM study in 1996 concluded overall that that finasteride is acceptably safe when used in accordance with the current prescribing information.** However, it is not possible from this study to evaluate the cases of breast cancer and their causal relationship with finasteride, as enough data is not available regarding the 2 events of breast carcinoma.

In 1998, McConnell and colleagues published the Proscar long term efficacy and safety study (PLESS). There were 3,040 patients were followed up for a period of 4 years. The patients were randomized in approximately equal proportions to receive either 5 mg finasteride or placebo for up to 4 years. **In this study, there were no cases of male**
breast cancer reported in finasteride-treated subjects, and 2 cases were reported in placebo-treated subjects.

2012-2017 PUBLISHED STUDIES ON SPIRONOLACTONE AND BREAST CANCER

In 2017, McKenzie studied the risk of cancer among users of Spironolactone. The participants were 74,272 patients exposed to spironolactone between 1986 and 2013 using the Clinical Practice Research Datalink from the UK. In this study, there was no increased risk of cancer in spironolactone users.

In 2013, Biggar published data specifically looking at the risk of breast cancer in female Spironolactone users. The researchers used a nationwide prescription drug registry between 1995 and 2010 and identified use of spironolactone in a cohort of Danish women (≥20 years old). After studying 2.3 million women (28.5 million person-years), the authors concluded that with respect to breast, uterus, ovarian and cervical cancer, there is no evidence of increased risk with spironolactone or furosemide use.

In 2012, McKenzie published a study a retrospective cohort study evaluating whether exposure to spironolactone treatment affects the risk of incident breast cancer in women over 55 years of age. The study involved 1,290,625 female patients, older than 55 years and with no history of breast cancer, from 557 general practices with a total follow-up time of 8.4 million patient years. Although the vast majority of women were using doses under 100 mg, 17.2% of women in the study were using 100 mg doses and 3.6% were using 200 mg doses. The data suggested that the use of spironolactone did not increase the risk of breast cancer. The exposed cohort of 28,032 patients and control cohort of 55,961 patients had unadjusted incidence rates of 0.39% and 0.38% per year, respectively. There was no evidence of an increased incidence of breast cancer in patients exposed to spironolactone (hazard ratio 0.99, 95% confidence interval 0.87 to 1.12).

Based on this information, we don’t really have good evidence to suggest that Finasteride causes breast cancer or that Spironolactone causes breast cancer. What we are less certain of is whether there is in fact an increased risk of cancer for women at higher risk for breast cancer who uses these drugs.
If one’s risk of breast cancer is greatly elevated the information below regarding risk does not apply because the information below pertains to individuals with low risk levels for breast cancer. **We do not have information about the risk of breast cancer in women at highest risk who use anti-androgens. The only information we really have pertains to patients at lower risks.** In particular, we don’t have information on women with genetic susceptibilities to breast cancer who use anti-androgens. **This must be weighed carefully against the nearly certain risk of irreversible and progressive hair loss with stopping anti-androgens.**

My advice for patients with elevated risk who wish to use anti-androgens would be to have a discussion with an oncologist. Once needs to consider fully the estimated risk for breast cancer, the risk for ongoing hair loss and the chance of success of other therapies

**REFERENCES**


2. Wiebe JP, et al. Progesterone-induced stimulation of mammary tumorigenesis is due to the progesterone metabolite, 5α-dihydroprogesterone (5αP) and can be suppressed by the 5α-reductase inhibitor, finasteride. J Steroid Biochem Mol Biol. 2015.


Question 25. A 31 year old female with alopecia totalis has experienced partial regrowth with tofacitinib 5 mg twice daily. She has been tolerating the drug quite well and is now considering increasing to 10 mg twice daily. Which of the following side effects could potentially be increased by doubling the dose?

A. Increased risk of hyperlipidemia
B. Increased risk of infection
C. Increased risk of pulmonary embolism
D. All of the above

ANSWER: D, All of the above.

COMMENTS AND DISCUSSION

Tofacitinib is an inhibitor of the janus kinase 1 and janus kinase 3 and is FDA approved for the treatment of adults with moderate to severe rheumatoid arthritis, active psoriatic arthritis, and moderate to severe ulcerative colitis. It is sometimes used as off label treatment for alopecia areata. The typical doses in alopecia areata are 5 mg twice daily. For those patients who are only partial responders to the drug, a decision is sometimes made to increase doses to 15 and 20 mg and sometimes even higher (25 mg). As with any drug, the potential for side effects often increases with higher doses of a medication.

The following side effects of tofacitinib seem “dose dependent” - meaning that a greater proportion of people using the drug are expected to experience these side effects at the higher doses compared to the lower doses.

<table>
<thead>
<tr>
<th>DOSE DEPENDENT TOFACITINIB SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Elevation in Cholesterol</td>
</tr>
<tr>
<td>2. Elevation in Creatinine</td>
</tr>
<tr>
<td>3. Herpes Zoster Infections</td>
</tr>
<tr>
<td>4. Serious Infections</td>
</tr>
<tr>
<td>5. Non-melanoma skin cancer</td>
</tr>
</tbody>
</table>
During the last week of February 2019, the company Pfizer made an announcement that patients with rheumatoid arthritis who use higher doses of tofacitinib with their methotrexate may be at increased risk for pulmonary embolism (blood clots in the lungs). Pfizer reported an update from their study known as “A3921133” which is a study that allows surveillance of potential side effects in the years after the drug is launched to the public. Study A3921133 was designed to evaluate the safety of tofacitinib at two doses (5 mg twice daily and 10 mg twice daily) and compare side effects to patients using a tumor necrosis factor inhibitor (TNFI). This study was designed to assess the risk of cardiovascular (CV) events. In this particular study, patients were required to be at least 50 years of age and have at least one CV risk factor to be eligible for participation in this study. All patients entered the study on stable doses of the immunosuppressive drug methotrexate. The data safety monitoring board that oversees that study observed that patients treated with tofacitinib 10 mg twice daily had a statistically and clinically important difference in the occurrence of pulmonary embolism, compared with patients in this study who were treated with a TNF inhibitors. The DSMB also noted an increase in overall mortality in the 10 mg twice daily treatment group compared to the tofacitinib 5 mg twice daily and TNFI treatment arms.

As a result of this study, Pfizer took steps move rheumatoid arthritis study patients who were on tofacitinib 10 mg twice daily down to tofacitinib 5 mg twice daily.

**High Dose Tofacitinib in Alopecia Areata**

This update from the A3921133 study is important because it reminds us that as we increase the dose of any drug, we need to let patients know what side effects might be experienced on these higher doses compared to staying on the lower doses.

The patients in the A3921133 study were slightly older and had heart disease to begin with and were using methotrexate. When faced with a patient with alopecia areata who is older than 50 and has heart disease and is using methotrexate, it is most certainly appropriate to advise them that increasing their tofacitinib dose from 10 mg to 20 mg might increase their chances of having a blood clot in the lung.

What we don’t know now is whether the typical patient with alopecia areata (who is generally very healthy) is at increased risk for a blood clot with higher doses of tofacitinib. Is that 21 year old very healthy college student who failed nearly every other drug we tried but who is doing amazing well now on 20 mg of tofacitinib placing themselves at increased risk for a blood clot? That we simply don’t know. Nevertheless, it is important that good studies and monitoring specifically in patients with alopecia areata be done. For now, it would at least be appropriate to keep this side effect on our radar.

**REFERENCE**