TrichoConcept™

The first line of personalized treatment for alopecia

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personalizing medicine

Summary

1. INTRODUCTION

Alopecia is a chronic dermatological disorder characterized by partial or complete hair loss from one or more body areas, most commonly affecting the scalp (Figure 1).[1] It can be related to systemic conditions, such as autoimmune or endocrine diseases, chronic infections, and nutritional deficiencies.[2]

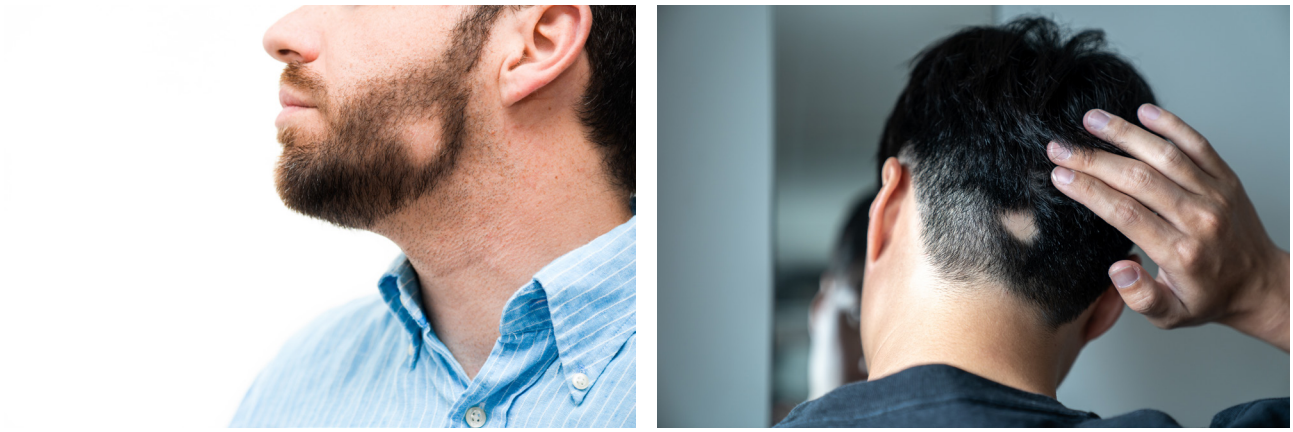


Figure 1. Hair loss: (left) involving the face; (right) involving the scalp.

In addition, alopecia can have an acute onset or be a slowly progressive disease. A lack of accurate diagnosis and treatment can lead to reduced patient compliance and, most importantly, to the non-identification of clinically important conditions.[3]

Detailed patient history and physical examination are crucial to distinguish between different types of alopecia, which can be categorized primarily into two subtypes: nonscarring (non-cicatricial) and scarring (cicatricial).[2]

Nonscarring alopecia refers to the follicular unit patency that remains intact during the progression of the disease. It can be focal or diffuse, which means that it can involve patches of hair loss or the entire scalp, respectively.[4] Therefore, treatment is focused on the restoration of hair growth.[5] Nonscarring alopecia include Androgenetic Alopecia, Alopecia Areata, Telogen Effluvium, and Traction Alopecia (Figure 2).[4,6,7]

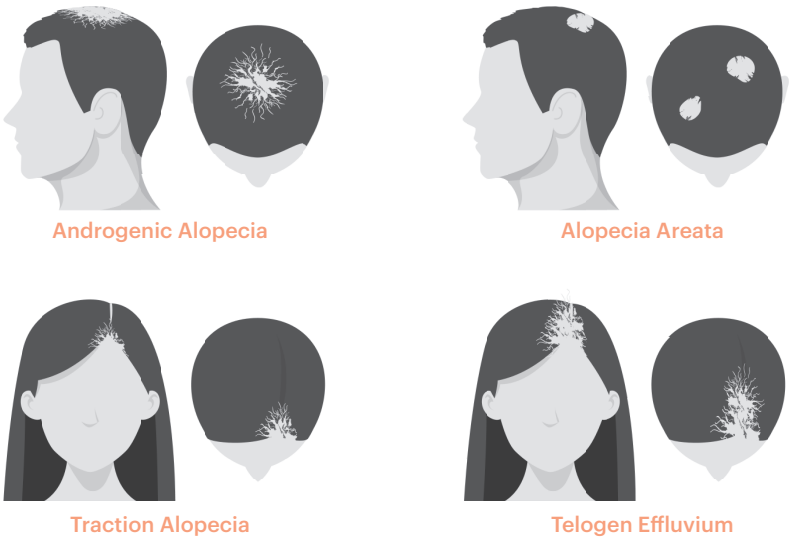


Figure 2. Types of Nonscarring Alopecia.

Scarring alopecia is a rare condition that leads to the complete destruction of the hair follicle. Consequently, it represents irreversible hair loss, and treatments aim to diminish inflammation and prevent future worsening of the pathology. Scarring alopecia include Lichen Planopilaris, Frontal Fibrosing Alopecia, and Central Centrifugal Cicatricial Alopecia.[8]

Despite the clinical aspects, studies have demonstrated that alopecia affects patients' quality of life, self-esteem, and psychological well-being.[9] For example, psychiatric disorders, such as depression and anxiety, are mainly reported among patients with hair loss compared to the general population.[10] For that reason, early diagnosis and treatment are crucial to optimize the course of the disease.

Commercially available topical options for hair growth are still limited, with minoxidil being the most prescribed topical treatment on the market.[11–13] Though minoxidil is considered a successful treatment option, not all patients experience satisfactory outcomes.[13] Therefore, other Active Pharmaceutical Ingredients (APIs) with different mechanisms of action must be examined; additionally, adequate vehicles to apply these APIs on the scalp play an essential role in patients' adherence to treatments, contributing positively to achieving excellent outcomes. An in-depth understanding of the hair growth cycle is needed to prevent or better treat hair loss.[14] To fulfill individual needs and optimize health outcomes, Fagron developed the **TrichoConcept™** line.[15]

Fagron's **TrichoConcept™** is the first global line of multifunctional compounding vehicles with the **TrichoTech™** technology, a Fagron patented phytocomplex specially developed for use in personalized alopecia treatment.[15] This brochure describes the hair growth cycle, the most common types of alopecia, and how the **TrichoConcept™** line can play an important role in their personalized treatment.

2. THE HAIR STRUCTURE

2.1. Histology of the Hair

The hair is a natural, elastic, high-strength fiber from the corneal epithelium. Its growth is supported by rich blood irrigation of its roots, with a growth rate as high as 0.33 mm per day, equivalent to 1 cm per month (or 10–15 cm per year).[16]

Histologically, the hair fiber includes the following structures from the outside to the inside (Figure 3):[16]

- **Cuticle**: Similar to cohesive scales, totally keratinized cells in the shape of platelets arranged lengthwise to the hair shaft. In healthy hair, these scales are flush with the hair shaft; in traumatized hair, they are irregular and rough. The arrangement of these scales is directly related to the ease of combing, as well as tangling, shine, and general appearance.
- **Cortex**: The central part of the hair fiber, formed by keratinized spindle cells (keratin has a negative charge, which allows the retention of positively charged substances) and contains melanin granules that give the hair its color. It is formed by macro- and microfibrils of alpha keratin; these filaments provide both elastic and mechanical properties. The cortex is where bleaches, straighteners, permanents, and some dyes take effect.
- **Medulla** (medullary canal): Essentially formed by anucleated cells, but also containing lipids and pigments in addition to the occasional inclusion of air.

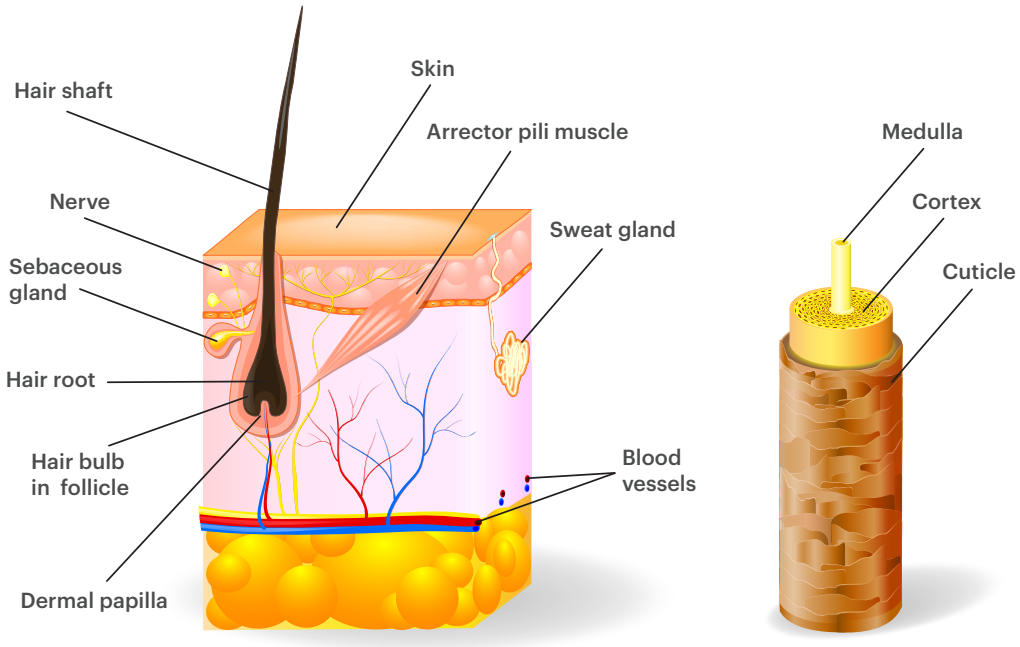


Figure 3. Hair anatomy, showing the main structures.

The hair follicle structure and growth cycle are greatly influenced by various hormones, of which androgens are the most pronounced.[17] They act on sex-specific body areas, converting tiny and straight hairs into more prominent, darker terminal hairs. Additionally, most hair follicles require the intracellular enzyme 5-alpha reductase to convert testosterone into dihydrotestosterone, a crucial factor in terminal hair growth.[18] Although growth and loss of hair may seem a simple process, the hair growth cycle has been a matter of debate. Classically, it is divided into three phases: the growing phase (anagen), the regression phase (catagen) and the resting phase (telogen).[19]

2.2. Hair Growth Cycle

Anagen is the most prolonged phase, lasting from 2-7 years. It is also known as the growing phase. During this phase, cells divide rapidly at the lower part of the hair while matrix cells migrate outward.[20] Catagen is a short transition phase, lasting around three weeks. The hair stops growing and becomes detached from the base of the follicle. The hair bulb begins to break down, making the follicle shorter.[21] On average, 1% of follicles are in the catagen stage. Lastly, telogen is the resting phase and can last about three months. During this phase, the hair does not grow but stays attached to the follicle.[19] Approximately 10–15% of all hair is in the telogen phase. At the end of this phase, the hair follicle reenters the anagen phase and new hair begins to form. This progress from one phase to another can be explained by dynamic events between the dermal papilla and the extracellular matrix around the bulge (Figure 4).[19–21]

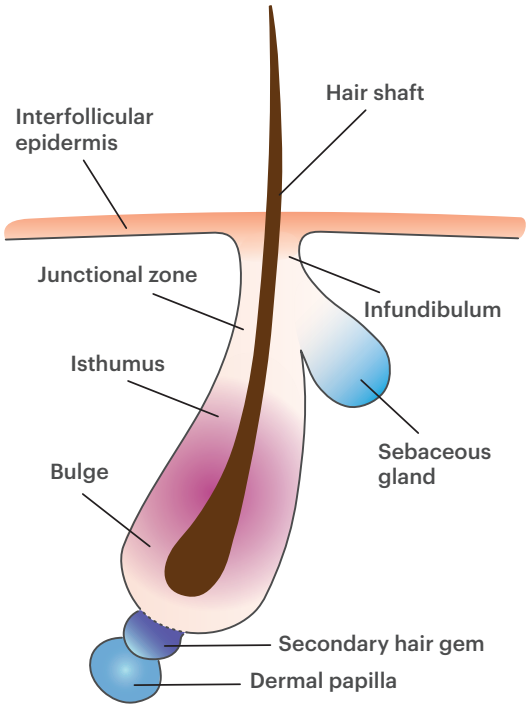


Figure 4. Hair follicle structure.

A phase known as "exogen" has been described as an additional distinct phase in which the active hair shaft and new hair continue to grow.[22] Between the elimination of a hair fiber in the exogen phase and the appearance of a replacement hair in the anagen phase, a latency period is observed in 80% of hair cycles – the kenogen period. In addition, it was proposed that if the regression phase is termed "catagen", the regeneration phase should be termed "neogen".[23] Therefore, the hair cycle would include four main successive phases: anagen (fiber production), catagen (regression), telogen (resting), and neogen (regeneration) (Figure 5).[22,23]

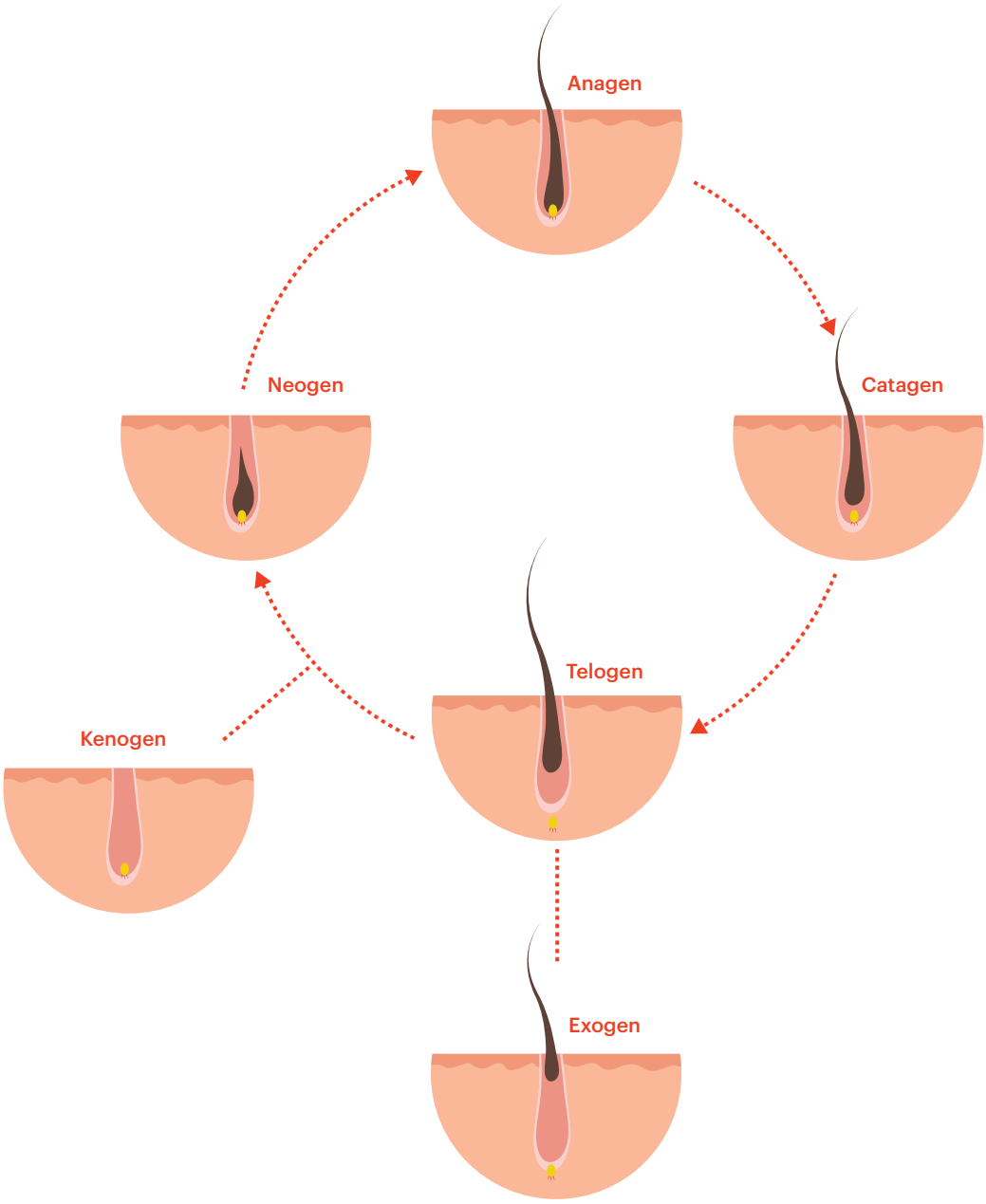


Figure 5. Hair growth cycle.

3. ALOPECIA TYPES AND TREATMENTS

3.1. Androgenetic Alopecia

Androgenetic alopecia (AGA), also known as male or female pattern hair loss, is the most prevalent form of progressive hair loss, affecting 70% and 50% of middle-aged men and women, respectively.[1] It is characterized by non-scarring progressive hair follicle miniaturization with a pattern distribution.[2] Clinically, it manifests as thinning along the scalp vertex and bitemporal hairline with relative sparing of the occipital scalp as well as a recession of the frontal hairline in men (Figure 6). Contrarily, in women, it manifests as a diffuse hair thinning over the central scalp, but the frontal hairline is usually preserved (Figure 7).[24]

Figure 6. Androgenetic alopecia in man.

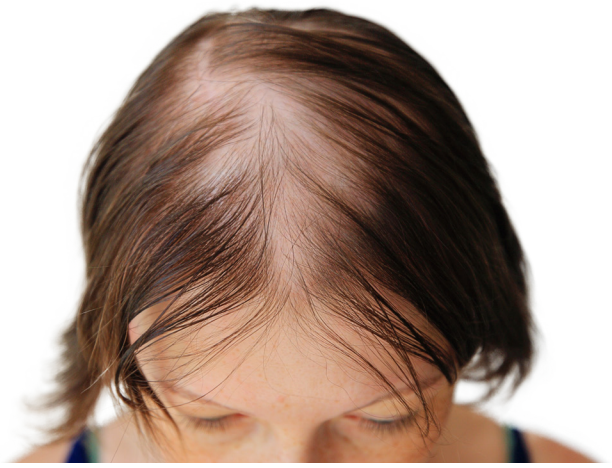


Figure 7. Androgenetic alopecia in woman.

Although multifactorial, the causes of AGA are mainly related to an increase in dihydrotestosterone (DHT), a metabolite of testosterone.[25] This results from an alteration in hair cycle dynamics: the anagen phase duration gradually decreases and the telogen phase increases. As the anagen phase duration determines hair length, the new anagen hair becomes shorter, eventually leading to a bald appearance.[26]

The AGA treatment depends on different factors, such as efficacy, practicability, risks, and costs. The aim is to prevent the miniaturization process and, if possible, reverse it.[27] Minoxidil, currently the first-line topic treatment, has a good safety and efficacy profile; however, many patients prematurely discontinue treatment.[13] Undesirable hair texture, scalp irritation, and the frequency of application have been associated with this poor compliance.[28–30]

Most commercially available topical minoxidil formulations contain excipients such as parabens, propylene glycol, artificial colorants, and high concentrations of alcohol, potentially leading to scalp irritation and undesirable side effects.[31] Additionally, different minoxidil concentrations have been prescribed, and variable treatment responses have been reported.[12] Therefore, personalized medicine has bridged the gap between standard treatments and individual patients' needs.[14,15]

3.2. Alopecia Areata

Alopecia Areata (AA) is an autoimmune condition characterized by non-scarring hair loss, affecting approximately 2% of the general population.[4] The pathogenesis remains not fully known but includes autoantibodies acting directly against the hair follicle, specifically at structures in the anagen phase, leading to hair loss.[32] Additionally, AA has been associated with other diseases, such as rheumatoid arthritis, lupus erythematosus, psoriasis, vitiligo, and thyroid disease.[33]

The clinical presentations vary from well-defined patches to diffuse or total hair loss and have been categorized into several subtypes, including AA patch-type, ophiasis, totalis, and universalis.[34] The patch-type presents as small, well-circumscribed alopecic patches, while the ophiasis manifests as a

symmetric, bandlike hair loss involving the occipital, parietal, and temporal areas of the scalp (Figure 8).[35] Alopecia totalis is characterized by the complete or near-complete loss of hair on the scalp, while alopecia universalis presents as total hair loss affecting all hair-bearing sites, for example, scalp, eyebrows, eyelashes, axillary hair, and pubic hair.[36]

Figure 8. Patch-type alopecia areata.

Furthermore, although AA is self-limited, it can last several months or even years in some patients.[32] Treatment options include topical and intralesional corticosteroids, topical minoxidil, and phototherapy for limited manifestations. For more extensive cases, such as alopecia totalis and universalis, systemic corticosteroids, intramuscular corticosteroids, methotrexate, and cyclosporine have been used.[4] However, the response rates and prognosis for hair regrowth are widely variable among patients.[37]

3.3. Telogen Effluvium

Telogen effluvium is a nonscarring form of alopecia characterized by diffuse, often self-limited hair shedding. It usually occurs around three months after a triggering event that affects the normal hair cycle and lasts for about six months.[38] Telogen effluvium happens when hair follicles prematurely enter the telogen phase or when the telogen phase is shortened, subsequently leading to excessive shedding of these hairs.[2]

Typical triggering events are metabolic stress, i.e., major surgery and severe infection; hormonal changes, i.e., hypothyroidism and postpartum phase; and medications, i.e., beta-blockers, retinoids, anticoagulants, and immunizations.[39] The prevalence of telogen effluvium is challenging to estimate, but it can occur in people of any age, gender, or ethnic background. Although it can happen in both sexes, women are more likely to experience this condition.[40]

As telogen effluvium is considered a diagnosis of exclusion, a detailed patient evaluation is needed.[2] The time course of hair loss, stressful events, and medication changes are crucial information to rule out other causes of hair loss.[41] Additionally, thyroid and iron laboratory tests should be considered when no apparent triggers for telogen effluvium were evident in the patient's history.[38]

Telogen effluvium typically resolves spontaneously within six months of onset. Therefore, the expectant treatment is usually appropriate in most cases.[40] However, when a potential underlying cause is identified, the condition should be treated and managed accordingly.[2]

3.4. Traction Alopecia

Traction Alopecia results from prolonged or repeated tension on the hair root linked to specific hairstyling practices.[2] It's highly prevalent among patients of African ethnic background; however, it can be present in any patient.[42,43] The excess tension on the hair causes mechanical damage to hair follicles, such as inflammation and miniaturization, consequently leading to hair loss. The early signs and symptoms of excess tension include pain, stinging, pimples, tenting (raising of the skin on the scalp), and crusting in the scalp.[44] Although traction alopecia is primarily a non-cicatricial and reversible disease, chronic trauma to the scalp can lead to permanent cicatricial hair loss in the affected areas.[45]

Clinically, it manifests along the frontal or bitemporal region of the hairline (Figure 9).[46] Depending on the stage of the alopecia, different characteristics can be observed in histopathology. An increased number of telogen and catagen hair follicles is observed in the early stage.[45] In later stages, there is a decrease in the terminal follicle count which is replaced with fibrotic fibrous tracts.[44]

Treatment's first step includes encouraging loose hairstyling options allowing hair regrowth, and preventing progressive damage.[43] If there is evidence of active inflammation in the scalp, medications such as topical minoxidil, intralesional corticosteroids, and topical or oral antibiotics might be needed.[42] Within months, complete restoration of hair growth can occur in patients with early stage alopecia who discontinue harmful styling habits.[2]

Figure 9. Traction alopecia.

3.5. Alopecia Common Treatments and Strategies

Traditional treatments for alopecia can be divided into different groups based on their therapeutic effects: [47–49]

- Prostaglandin analogs: they are a group of molecules with a hormone-like effect, mainly used in androgenetic alopecia and alopecia areata. E.g., Prostaquinon™, latanoprost, and minoxidil.
- Anti-androgens: a class of APIs that prevent androgens from mediating their biological effects in the body. They are mostly used in androgenetic alopecia. E.g., finasteride, dutasteride, caffeine, 17-α-estradiol.
- Anti-inflammatories: mainly corticosteroids, they are analogs of steroid hormones with anti-inflammatory, immunosuppressive, anti-proliferative and vasoconstrictive effects. These treatments are mainly used in alopecia areata. E.g., desonide, hydrocortisone, clobetasol propionate, triamcinolone acetonide.
- Vasodilators: they widen blood vessels, allowing for improved blood flow, and they can benefit all types of alopecia. E.g., minoxidil, caffeine, *Ginkgo biloba*.

- Collagen synthesis stimulators: APIs and dermaceutical ingredients (DCIs) that stimulate collagen synthesis in all types of alopecia. E.g., cystine, silicium (as maltodextrin-stabilized orthosilicic acid - SiliciuMax® powder; monomethylsilanetriol - SiliciuMax® liquid), adenosine.
- Vitamins and minerals: to restore and rebalance vitamin deficiencies, benefiting all types of alopecia. E.g., biotin, nicotinamide, retinol, selenium yeast, coenzyme Q10, pyridoxine, α-tocopherol.
- Insuline-like growth factors: they stimulate keratinocytes proliferation, in addition to their anti-apoptotic effect and delay at the beginning of the catagen phase. Mainly used for androgenetic alopecia and alopecia areata. E.g., IGrantine-F1™.
- Immunosuppressors: APIs that inhibit or prevent exacerbated immune system activity in alopecia areata treatment. E.g., clobetasol propionate, hydrocortisone acetate, triamcinolone acetonide, tacrolimus.

Alopecia treatments can have a systemic (oral) or local (topical) approach, depending on the severity of the condition or on the patient's profile. This material focuses primarily on topical treatments, discussing the importance of combining different APIs with adequate compounding vehicles.

As important as the chosen APIs or DCIs in alopecia treatments, the vehicle where they are incorporated plays a crucial role in achieving successful therapeutic outcomes.

Usually, vehicles used in hair and scalp treatments are formulated with ingredients such as alcohol, propylene glycol and other solvents that, on the one hand, help to solubilize the API in the product, but on the other hand, can be irritant to the scalp and cause dryness to the skin and the hair, damaging its structure.

Additionally, adequately formulated vehicles can help maintain the hair system's physiology. Therefore, topical treatments can be positively affected, as a healthy scalp may present a superior capacity for APIs absorption.

Until now, there is a limited choice of vehicles that are at the same time compatible with APIs used to treat alopecia. Also, depending on the symptoms onset, multiple APIs and DCIs may be applicable during treatment, and compounded formulations allow the strategic combination of those. For this reason, Fagron has developed **TrichoConcept™**.

The **TrichoConcept™** is a global line of multifunctional compounding vehicles specially developed for patients undergoing alopecia treatment, providing a safe and validated alternative to traditional vehicles containing controversial and aggressive ingredients. Fagron's **TrichoConcept™** uses the patented **TrichoTech™** technology, a phytocomplex developed with selected ingredients that aid multiple benefits to the bulb, scalp and shaft (BSS) hair system.

4. TRICHOTECH™

Essential oils are commonly present in hair and scalp products, such as shampoos, conditioners, repair serums, foams, among others, and their beneficial effects include anti-inflammatory and anti-fungal activities, reduction of scalp irritation, dandruff and oiliness control, hair follicles and hair growth stimulation, and improvement in local blood circulation.[50]

TrichoTech™ is a patented and unique phytocomplex developed with carefully chosen essential oils that act synergistically on the scalp, providing multiple benefits to the BSS hair system. The oils in **TrichoTech™** are extracted from an exclusive cultivation chain with enriched soil that ensures the highest quality with standardized chemical markers.

The synergy of essential oils results from the combination of their therapeutic properties that, once combined, do not only aggregate but also potentialize each other, creating a new range of interactions.[51] To achieve the maximum synergistic effect, the essential oils in **TrichoTech™** were selected based on their chemical components and combined in the most adequate concentration to strengthen their therapeutic effects. **TrichoTech™** is present in all **TrichoConcept™** vehicles.

4.1. The TrichoTech™ functional ingredients

Lavandula angustifolia Mill

The *Lavandula angustifolia* (lavender) oil is rich in monoterpenes and organic acids, mineral salts, tannins and coumarins, which are responsible for its pharmacological activities.[50,52] Traditionally, lavender oil has been widely used in aromatherapy with multiple applications.[52] In dermatology, its application includes psoriasis, dermatitis, and eczema; in trichology, it has shown positive results in patients with alopecia and dandruff, helping to restore hair growth and balance sebum production.[50,52,53]

Eucalyptus globulus Labill

The *Eucalyptus globulus* (eucalyptus) essential oil consists mainly of oxygenated monoterpenes, monoterpenes and oxygenated sesquiterpenes, but more than 50 substances can be found in its chemical composition.[50,54] Eucalyptus oil is widely known for its significant anti-inflammatory, analgesic and anti-fungal properties, with positive effects against dandruff on the scalp.[54,55] Additionally, it has been used in combination with other oils as a moisturizer and natural shine enhancer in hair products, also due to its pleasant aroma.[54]

Juniperus virginiana L.

Juniperus virginiana (red cedar) essential oil is rich in cedrenes, cedrol, widdrol, and sesquiterpenes, which contribute to its application for hair loss and dandruff.[56] Additionally, red cedar has been commonly described for its good antibacterial, anti-seborrheic, antiseptic and anti-inflammatory effects.[57]

Juniperus communis L.

Similarly to *Juniperus virginiana*, the *Juniperus communis* (common juniper) has excellent application in the cosmetic and dermatological fields as a complementary therapy for hair loss and dandruff.[58] Cedarwood oil can boost blood circulation in the scalp, stimulating hair growth. Additionally, it has benefits for dry hair and skin, inflammation, eczema, and also positive effects in seborrheic alopecia treatment.[50,58]

Melaleuca alternifolia

Melaleuca alternifolia (tea tree) oil, also known as melaleuca oil, has more than 100 chemical components (mostly monoterpenes), which have great antimicrobial, anti-inflammatory, and antioxidant activities. Melaleuca oil has been effectively used in a variety of skin and scalp disorders, including seborrheic alopecia and dandruff.[50,59]

Rosmarinus officinalis L.

One of the most used essential oils in aromatherapy, *Rosamrinus officinalis* (rosemary), is rich in substances such as 1,8-cineole, camphor, α-pinene, verbenone and borneol. Rosemary is largely known for its antibacterial, antioxidant and vasodilator, stimulating blood circulation (especially in areas such as the hair follicles).[50] Rosemary is a common ingredient in cosmetic hair products, feeding the hair follicles and providing moisture and strength to the hair.[60] It has also been used in patients with alopecia areata, with positive results in hair growth and hair loss prevention.[50,61]

Amyris balsamifera L.

The *Amyris balsamifera* is a plant from the Rutaceae family, and its essential oil has been previously studied for its antimicrobial activities.[62] Its main chemical components are valerianol, eudesmols, elemol and sesquiterpenes.[63] Amyris essential oil has also important antiseptic, calming, emollient and stimulant effects, encouraging skin regeneration and hydration, both topically and in the scalp.[64]

5. TRICHOCONCEPT™ - A LINE OF MULTIFUNCTIONAL VEHICLES

Essential oils are commonly present in hair products and the **TrichoConcept™** is the first global line of multifunctional compounding vehicles with the **TrichoTech™** technology. The vehicles were developed especially to use in alopecia treatment formulations, focusing on maintaining the physiology of the BSS hair system. When the physiology of the hair system is in good condition, it becomes more receptive to different treatments.

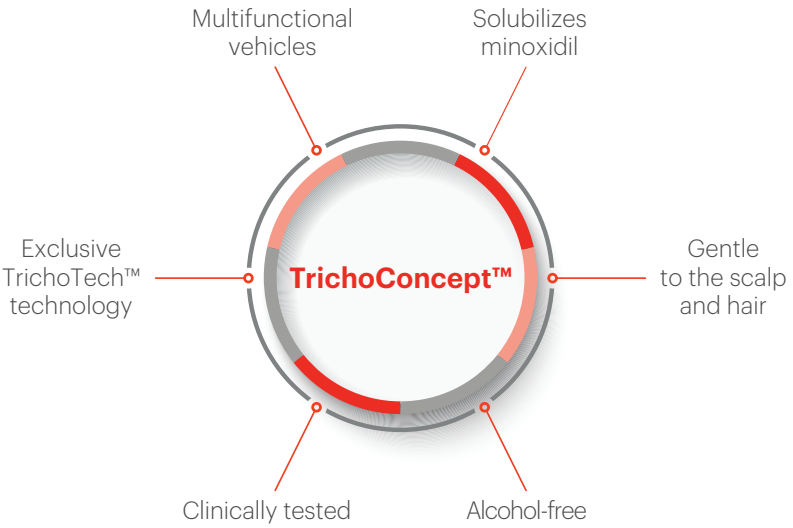
TrichoConcept™ vehicles were developed to be compatible with the majority of the APIs and DCIs used in alopecia treatment, allowing their easy incorporation into the vehicles.

There are seven different **TrichoConcept™** vehicles available, each one with exclusive characteristics according to the desired site or application. The vehicles can be grouped into two different categories:

Treatment of specific areas
- TrichoSol™
- TrichoFoam™
- TrichoCream™

Cleansing and care products
- TrichoOil™
- TrichoWash™
- TrichoCond™
- TrichoSerum™

The combination of vehicles from **TrichoConcept™** ensures adequate scalp preparation to receive the treatment, maintaining the proper surface pH, hydration and stimulating local blood circulation. Thanks to its selected ingredients, the **TrichoConcept™** line not only serves as adequate vehicles for compounding topical formulations, but also aids in functionalities that enhance the efficiency of treatments.



To maintain the physiology of the BSS hair system and avoid toxicity,
TrichoConcept™ vehicles are free from controversial ingredients that are frequently used in hair products:

- P — Parabens
- CH_2O — Formaldehyde
- PABA — P-Amino Benzoic Acid
- PO — Peanut Oil
- H_3BO_3 — Boric Acid
- BABB — Benzyl Alcohol Benzyl Benzoate
- PG — Propylene Glycol
- L — Lanolin
- TCS — Triclosan
- $C_4H_8O_2$ — 1.4-Dioxane
- MO — Mineral Oil Pertolatum
- AC — Artificial Colorants

TrichoSol™

TrichoSol™ is a highly spreadable hydrophilic solution containing mineral salts of vegetable origin. **TrichoSol™** formulation is gentle to the scalp, not causing the typical dehydration of hydroalcoholic solutions.

- Soft formula, gentle to the scalp
- Non-irritating vehicle
- Does not cause hair or scalp dryness
- Proven stability with water-soluble and liposoluble APIs and DCIs such as minoxidil, latanoprost and finasteride

TrichoSol™ can be applied directly in the affected areas, following the prescribed frequency of application according to the API and the designated treatment. A list of formulations with **TrichoSol™** can be found in the **TrichoConcept™** Formulary.

TrichoFoam™

TrichoFoam™ is a foaming vehicle, formulated with gentle, non-irritating and sensory-pleasant ingredients. **TrichoFoam™** is drip-free, allowing for a localized application of formulations, through a soft foam with minimal oiliness.

- Free from propellants
- Produces a soft foam with minimal oiliness
- Drip-free formulation
- Allows for localized application
- Proven stability with water-soluble and liposoluble APIs and DCIs such as Minoxidil

TrichoFoam™ can be applied directly in the affected areas, following the prescribed frequency of application according to the API and the designated treatment, being especially suitable for beard areas, as it is a drip-free vehicle. A list of formulations with TrichoFoam™ can be found in the **TrichoConcept™** Formulary.

TrichoSerum™

TrichoSerum™ is a soft and anti-frizz serum, that seals the hair cuticles maintaining its hydration, in addition to offering effective heat and color protection for chemically treated hair.

- Promotes hair brightness
- Anti-frizz action
- Heat and color protection

TrichoSerum™ can be applied to humid hair, after washing. Apply to the length of the hair and leave the product in. It can also be used before styling (blow-drying, following the prescribed frequency of application according to the API and the designated treatment, being especially suitable for beard areas, as it is a drip-free vehicle. A list of formulations with **TrichoSerum™** can be found in the **TrichoConcept™** Formulary.

TrichoCream™

TrichoCream™ is a natural hydrophilic gel cream based on olive oil and shea butter, with unique antioxidant and emollient properties. **TrichoCream™** is a non-greasy topical vehicle with adequate viscosity for safe local application in small areas, such as eyebrows and eyelids.

- Formulated with natural emulsifiers containing high concentrations of triglycerides of linoleic and oleic acids
- Contains tocopherol, providing an antioxidant effect for API protection
- Specially developed for application in eyelashes and eyebrows
- Non-irritant to the eye area

TrichoCream™ can be applied directly in the affected areas, following the prescribed frequency of application according to the API and the designated treatment, being especially suitable for eyebrows and eyelids. A list of formulations with **TrichoCream™** can be found in the **TrichoConcept™** Formulary.

TrichoOil™

TrichoOil™ is a 100% natural lipid vehicle that solubilizes liposoluble APIs and brings them to the BSS hair system through the lipid layer. **TrichoOil™** contains essential fatty acids that promote restoration and hydration of the scalp and shaft.

- Seals and strengthens the cuticle
- Replaces fatty acids in the hair fiber
- Restores and hydrates the scalp
- Ideal for the application of oil vitamins

TrichoOil™ can be applied on dry hair before washing. Spread the product from the hair roots to the tip, and let the product act for ten minutes. Wash the hair normally with **TrichoWash™** and **TrichoCond™**. Follow the prescribed frequency of application according to the API and the designated treatment. A list of formulations with **TrichoOil™** can be found in the **TrichoConcept™** Formulary.

TrichoWash™

TrichoWash™ is a shampoo developed with non-irritating ingredients, which cleans the hair and scalp without destroying natural fatty acids, promoting long-lasting hair hydration and softness. **TrichoWash™** delivers multiple benefits that favor the delivery of different APIs through the scalp, in addition to great antioxidant activity.

- Protects against visible signs of aging hair
- Replaces amino acids and proteins, favoring fiber repair
- Detoxifies hydrates and purifies the scalp
- Suitable for all hair types

TrichoWash™ can be applied on wet hair, as a common shampoo. Gently massage the scalp for two minutes and rinse with water afterward. Follow the prescribed frequency of application according to the API and the designated treatment. A list of formulations with **TrichoWash™** can be found in the **TrichoConcept™** Formulary.

TrichoCond™

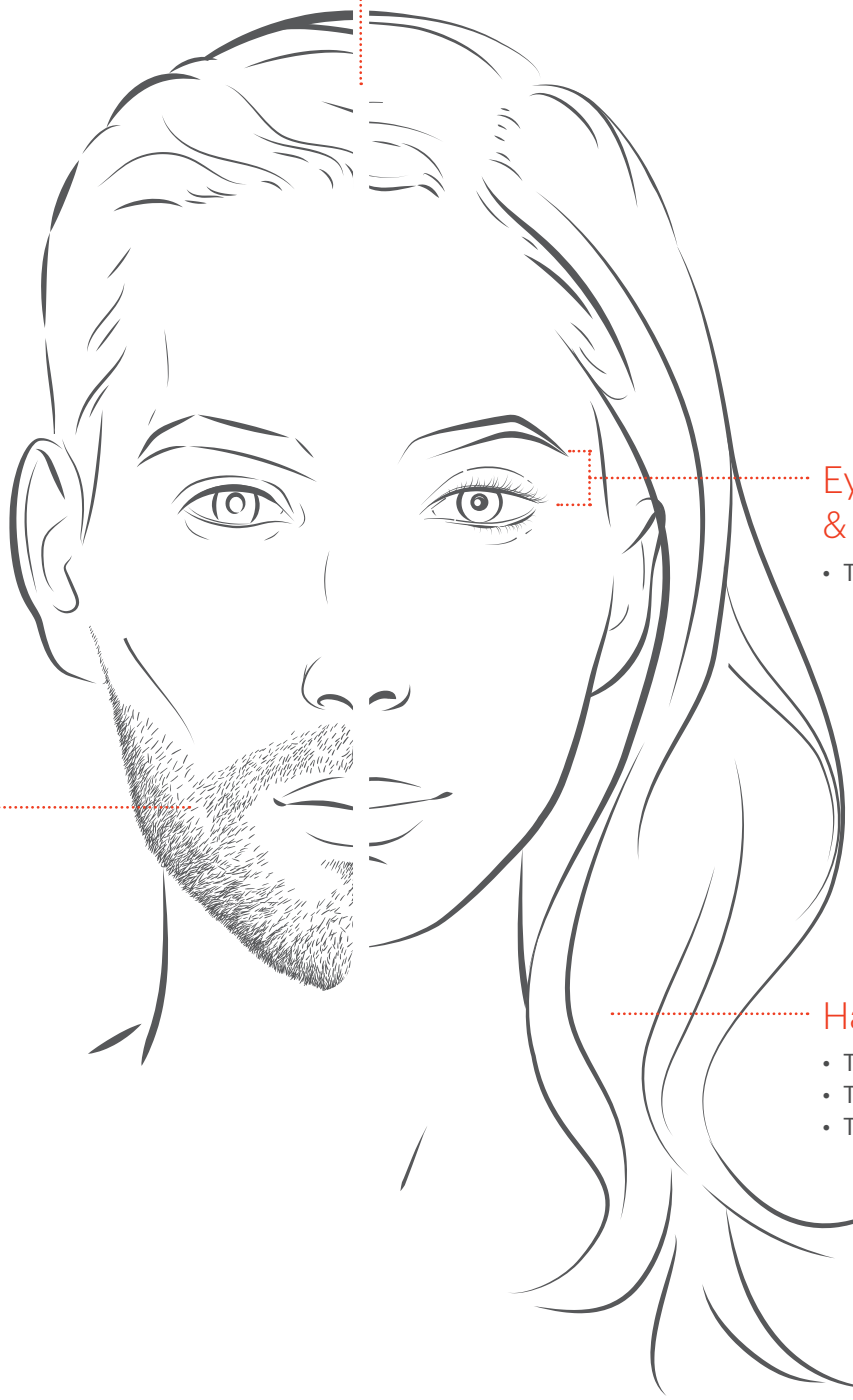
TrichoCond™ is a moisturizing conditioner with high hydration power to be specially used during hair treatment regimens. **TrichoCond™** balances the sebum production on the scalp, keeping the structure aligned and firm, and provides a source of essential peptides to maintain the hair cuticle. **TrichoCond™** regulates the isoelectric point of the hair, preventing cuticle breakage and cortex exposure. The adjusted pH of this vehicle also promotes the final cohesion of the hair cuticles.

- Reconstructs the cuticle
- Protects against visible signs of aging
- Replaces amino acids and proteins, favoring fiber repair
- Promotes cohesion, strengthening and hydration of the cuticle
- Non-greasy conditioner, suitable for all hair types

TrichoCond™ can be applied on wet hair, following the application of **TrichoWash™**. Apply along the hair length, leave it in for one to two minutes, and rinse with water afterward. Follow the prescribed frequency of application according to the API and the designated treatment. A list of formulations with **TrichoCond™** can be found in the **TrichoConcept™** Formulary.

Scalp

- TrichoSol™
- TrichoFoam™
- TrichoOil™
- TrichoWash™
- TrichoCond™



Eybrows & Eyelashes

- TrichoCream™

Beard

- TrichoSol™
- TrichoFoam™
- TrichoCream™

Hair Length

- TrichoWash™
- TrichoCond™
- TrichoSerum™

5.1. The Science Behind TrichoConcept™

5.1.1 TrichoTech™ *in vitro* studies

To evaluate the efficacy of **TrichoTech™**, a study was conducted to investigate its proliferative potential on cultured human fibroblasts and its ability to modulate the gene expression of FGF-7 and FGF-10 (fibroblasts growing factors), in an *in vitro* scratch in a cell monolayer.[65]

TrichoTech™ was shown to enhance fibroblast proliferation in concentrations of 0.5% to 2% (Figure 10). The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) colorimetric assay is an established method of determining the viable cell number in proliferation and cytotoxicity studies. **TrichoTech™** at concentrations of 1.5% and 2% significantly enhanced the proliferation of fibroblasts compared to the untreated group.

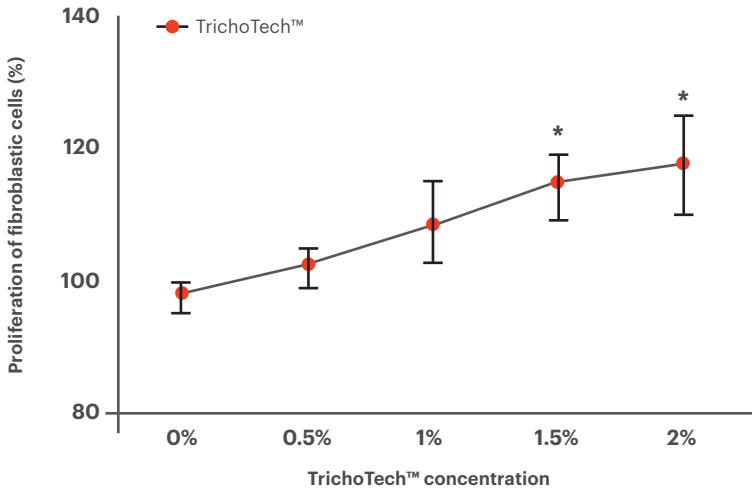


Figure 10. Cell proliferation results after 24 hours of exposure to different concentrations of **TrichoTech™**. (*)

Also, **TrichoTech™** increased the percentage of cells in the S/G2/M (synthesis, gap 2 and mitosis) phases of the cell cycle (Figure 11). The level of PI fluorescence in a cell is directly correlated to DNA content and its quantification indicates the percentage of cells in each phase of the cell cycle in a sample.

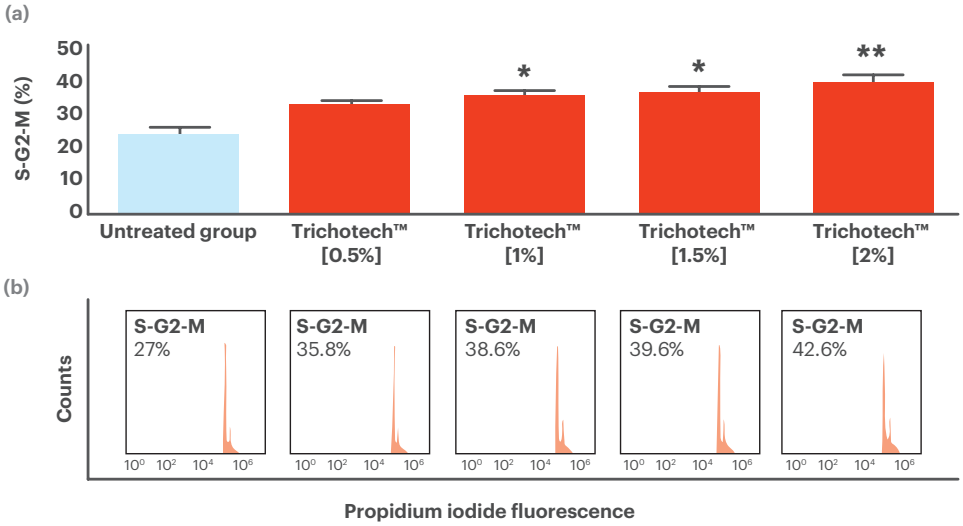


Figure 11. (a) Percentage of cells in S / G2 / M phase after 24 hours of exposure to different concentrations of **TrichoTech™**. (b) Representative histograms of proliferative activity. (*) p<0.05.

The *in vitro* scratch assay is a method to measure cell migration. To evaluate the wound healing capacity of **TrichoTech™**, scratches were made on confluent fibroblast monolayers, which were then exposed to **TrichoTech™** for 24 hours at two concentrations. **TrichoTech™** at both 1% and 2% induced a statistically significant effect on wound closure compared to the untreated control (Figure 12).

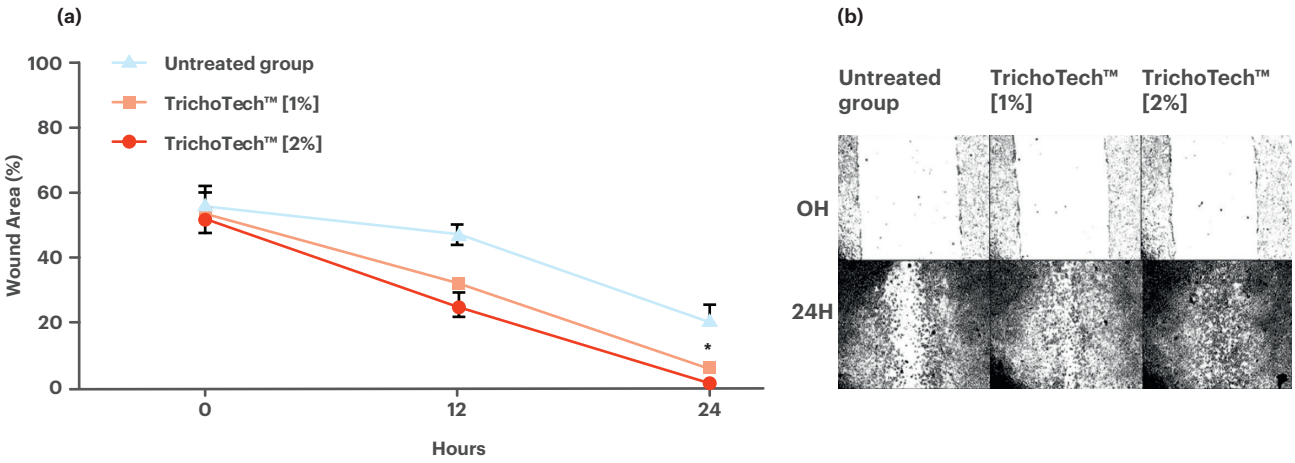


Figure 12. (a) Photographic representation of in vitro samples subjected to a simulated wound and exposed for 24 hours to different concentrations of **TrichoTech™**. (b) Representative graphic of the percentage of wounded area at 0 hours and 24 hours compared with an untreated group. (*) p<0.05.

The most highly studied intracellular signaling cascades in the context of cancer are the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/AKT pathways. The interaction between cell survival (PI3K/Akt) and mitogenic (Ras/ MAPK) signal transduction pathways, after adding **TrichoTech™** to the fibroblast cell line, was evaluated.

From the results obtained, **TrichoTech™** seems to promote the phosphorylation of ERK1/2 and MEK. The obtained results, together with the literature, suggest that **TrichoTech™** induces fibroblast proliferation possibly through upregulation of MAP kinase signaling pathways (Figure 13).

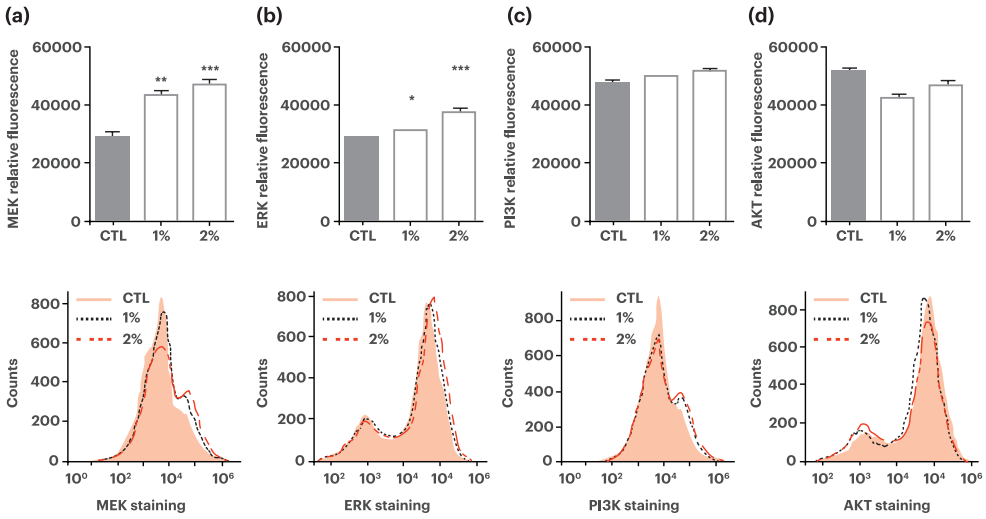


Figure 13. (Graphic and corresponding representative histogram of MEK (a), ERK (b), PI3K (c) and AKT (d) phosphorylated proteins signaling after one hour exposure to **TrichoTech™** 1% and 2%. Results are expressed by the MFI (median fluorescence intensity) and compared with the untreated group (CTL). (*) p<0.05.

Several growth factors (e.g., FGF-1, FGF-2, FGF-7 and FGF-10) have been reported as promoters of the cell cycle, cell proliferation and hair follicle regeneration both *in vivo* and *in vitro*. FGF-7 is expressed in the dermal papilla during the early anagen phase with its expression being down-regulated in late anagen. No FGF-7 RNA is usually detected in hair follicles during the catagen or telogen phase. FGF-10 is present in the dermal papilla and its receptor FGFR2IIIb is present in the neighboring outer root sheath of the keratinocytes, suggesting that FGF-10 is a mesenchymal-derived stimulator of hair follicle cells.

To verify the relative expression of mRNA for FGF-7 and FGF-10 genes, a real-time polymerase chain reaction (RT-PCR) protocol was used. Figure 14 shows the increase in mRNA expression by fibroblasts after treatment with **TrichoTech™**. In both concentrations tested, **TrichoTech™** was found to increase the expression of FGF-7 and FGF-10.

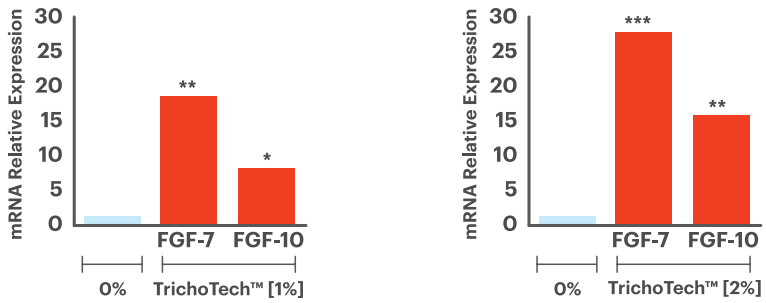


Figure 14. Relative expression levels of mRNA for FGF-7 and FGF-10 in human fibroblasts assessed by quantitative RT-PCR. (*) p<0.05, (**) p<0.01 and (***) p<0.0001.

Lastly, the total collagen content in fibroblasts was evaluated by the Sirius red staining method. The obtained results (Figure 15) reveal a significant increase in collagen content after the application of **TrichoTech™** in fibroblasts. The reported increase in collagen percentage between control and treated samples was markedly higher following treatment with **TrichoTech™** 2%.

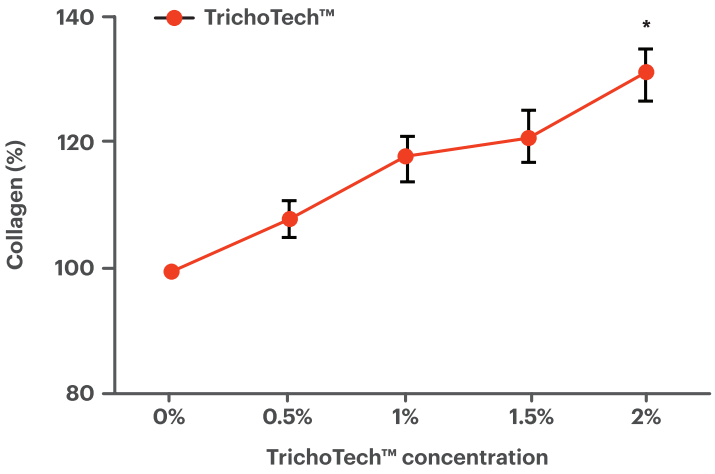


Figure 15. Total collagen content in fibroblasts, measured by the incorporation of Sirus Red dye after 24 hours of exposure to different concentrations of **TrichoTech™**. (*) p<0.05.

5.1.2 TrichoConcept™ *in vivo* studies

To evaluate the efficiency of **TrichoConcept™** as functional vehicles to improve alopecia treatments, a clinical study was performed with TrichoSol™.[66]

A comparison between the usage of **TrichoSol™** alone, **TrichoSol™** associated with minoxidil 3.0% and a traditional alcoholic minoxidil 3.0% solution was made, and their influence in the hair anagen phase was quantified through dermoscopy. All patient groups were treated for 90 days, in addition to the initial verification performed in the Trichoscan. Figure 16 shows an enlarged image of a patient at the time of the diagnosis (T0) and after the end of the study period (T90).

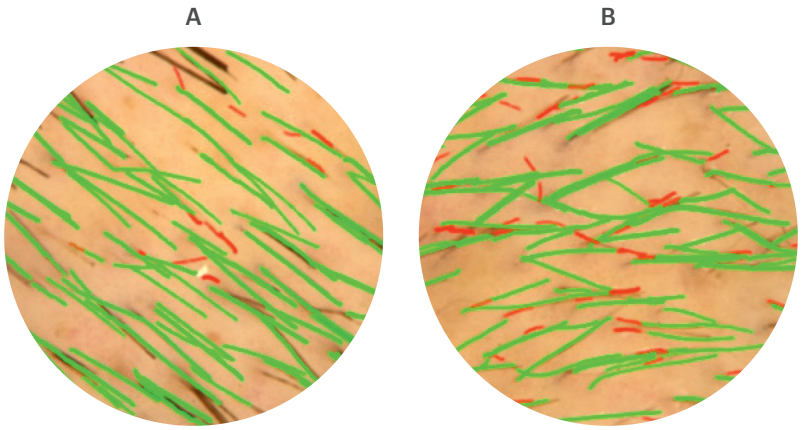


Figure 16. Trichoscan scalp image of a patient at T0 (A), indicating in red a small number of with wires in the anagen phase and T90 (B) after treatment with TrichoSol™ associated with minoxidil (3.0%), showing the increase of wires in the anagen phase (in red).

After data collection, the variation of the anagen phase was verified. Figure 17 shows the data analysis, comparing the variation of the percentage of anagen phase between the studied groups, with more than a 20% increase in the group treated with minoxidil 3% on TrichoSol™ in the anagen phase, when compared with untreated volunteers. Although not statistically significant, the group treated with minoxidil 3% and TrhicoSol™ was the one that most reduced the percentage of the telogen phase. Figure 18 shows the results obtained in both men and women.

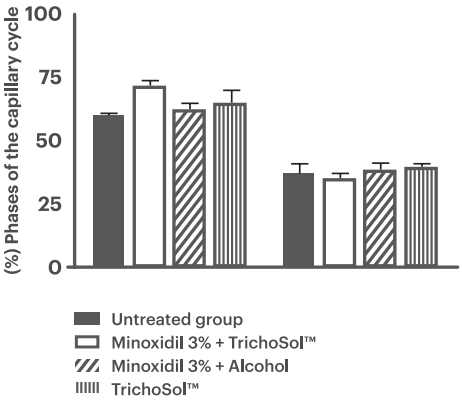


Figure 17. Data comparing treatment evolution and variations of the anagen and telogen phase in the volunteers treated with minoxidil 3% in TrichoSol™; minoxidil 3% in alcohol; TrichoSol™ and the untreated volunteers. There was a significant increase of about 20% in the anagen phase when compared with untreated volunteers.*p<0.05, ANOVA and Tukey's comparison.

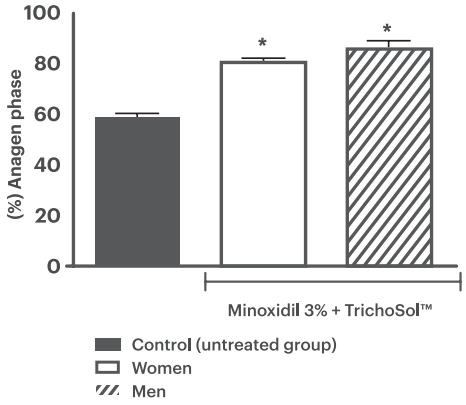


Figure 18. Control group without treatment versus groups of women and men treated with minoxidil (3%) in TrichoSol™ after 90 days.*p<0.05. ANOVA and Tukey's comparison.

The results of this study show that after 90 days of treatment with the combination of minoxidil 3% and **TrichoSol™** and with **TrichoSol™** alone, there is a significant increase in the percentage of hairs in the anagen phase, therefore showing that the **TrichoConcept™** is potentially beneficial in alopecia treatments.

5.1.3 TrichoConcept™ Case Reports

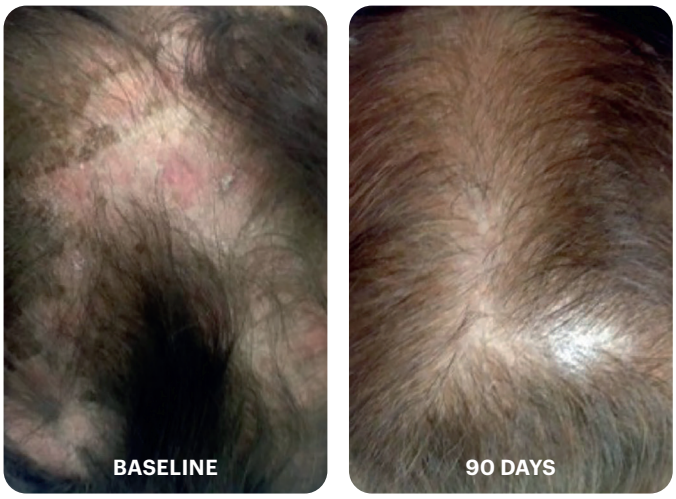


Figure 19. Hair shaft images before treatment (baseline), and after 90 days.

Case Report 1

Patient identification: M.R.S.L.
Gender: Female
Age: 69

Diagnosis
Chronic tinea capitis (Trichophyton tonsurans), combined with intense hair loss.

Treatment protocol
- Pre-treatment: terbinafine 250mg/day (6 weeks)
- TrichoOil™ (once per week)
- TrichoWash™ (daily)
- TrichoCond™ (daily)
- TrichoSol™ + Minoxidil 3.0% (daily)

Results
New hair growth and significant improvement in scalp inflammation were observed after 90 days of treatment with the **TrichoConcept™** protocol (Figure 19).

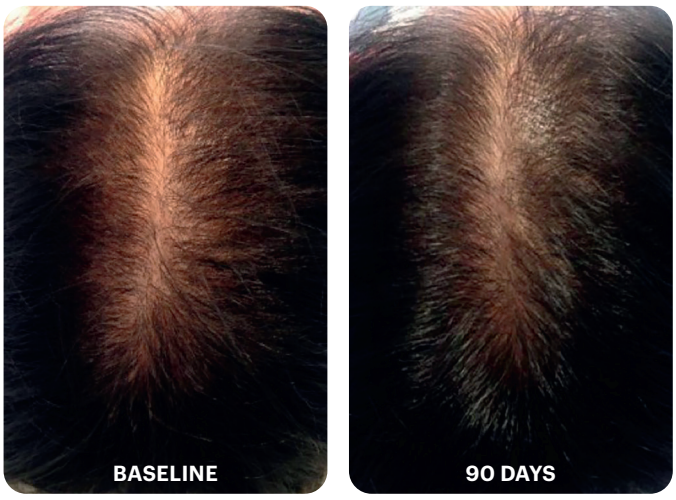


Figure 20. Hair shaft images before treatment (baseline), and after 90 days.

Case Report 2

Patient identification: C.S.C.
Gender: Female
Age: 26

Diagnosis
Androgenetic alopecia.

Treatment protocol
- TrichoOil™ (once per week)
- TrichoWash™ (daily)
- TrichoCond™ (daily)
- TrichoFoam™ + Latanoprost 0.005% (daily)

Results
New hair growth was observed after 90 days of treatment with the **TrichoConcept™** protocol (Figure 20).

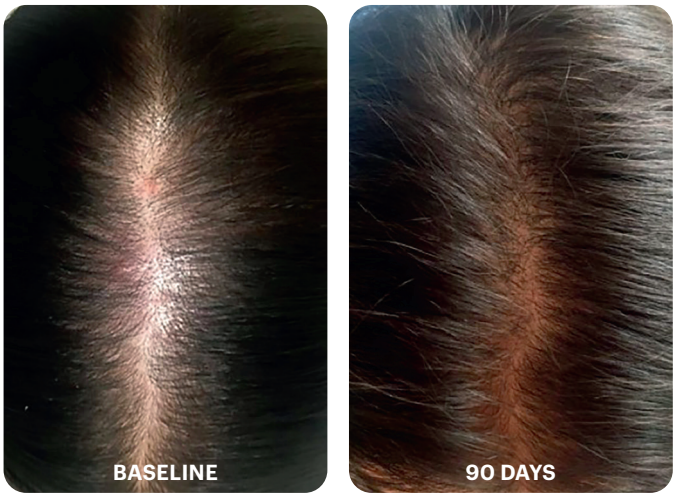


Figure 21. Hair shaft images before treatment (baseline), and after 90 days.

Case Report 3

Patient identification: F.P.M.
Gender: Female
Age: 23

Diagnosis
Androgenetic alopecia, irritant or allergic contact dermatitis.

Treatment protocol
- TrichoOil™ (once per week)
- TrichoWash™ (daily)
- TrichoCond™ (daily)
- TrichoSol™ + Minoxidil 3.0% (daily)

Results
New hair growth was observed after 90 days of treatment with the **TrichoConcept™** protocol (Figure 21).

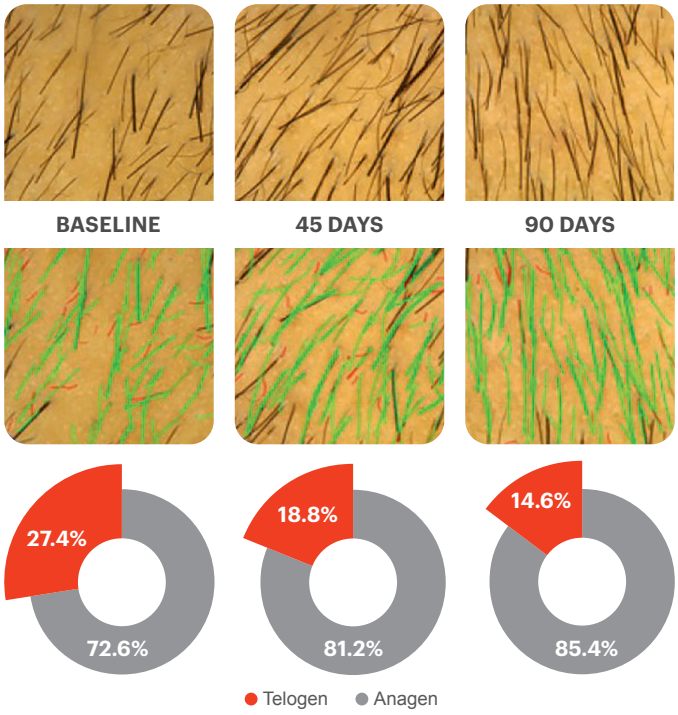


Figure 22. TrichoScan scalp images before treatment (baseline), after 45 and 90 days.

Case Report 4

Patient identification: M.V.L.B.S.
Gender: Female
Age: 53

Diagnosis
Androgenetic alopecia, telogen effluvium.

Treatment protocol
- TrichoOil™ + Prostaquinon™ 3.0% (once per week)
- TrichoWash™ (daily)
- TrichoCond™ (daily)
- TrichoSol™ + Latanoprost 0.005% (daily)

Results
After 45 days and 90 days, an increase in anagen hair was observed with the **TrichoConcept™** protocol (Figure 22).

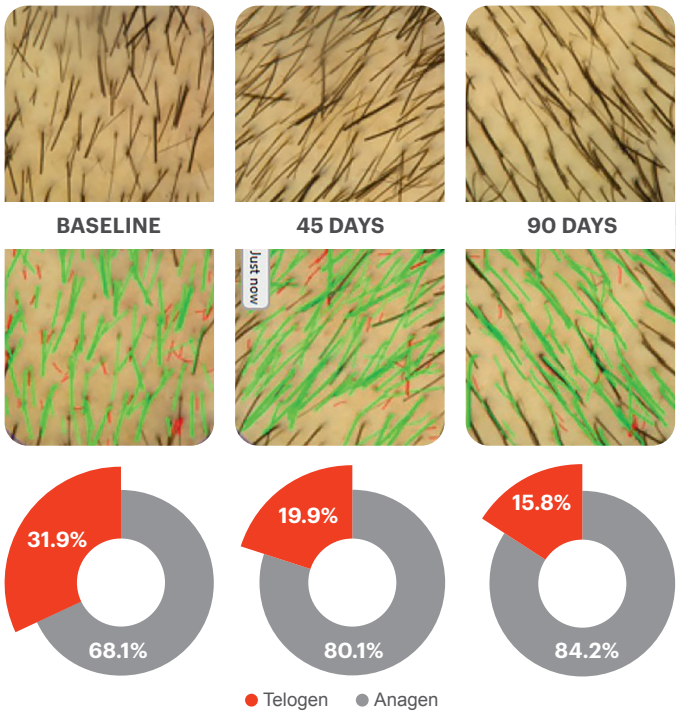


Figure 23. TrichoScan scalp images before treatment (baseline), after 45 and 90 days.

Case Report 5

Patient identification: P.G.M.
Gender: Female
Age: 34

Diagnosis
Telogen effluvium, androgenetic alopecia.

Treatment protocol
- TrichoOil™ (once per week)
- TrichoWash™ (daily)
- TrichoCond™ (daily)
- TrichoFoam™ + Minoxidil 3.0% (daily)

Results
After 45 days and 90 days, an increase in anagen hair was observed. The use of minoxidil associated with **TrichoConcept™** protocol showed effectiveness, even when this active ingredient was prescribed in percentage and posology lower than usual (Figure 23).

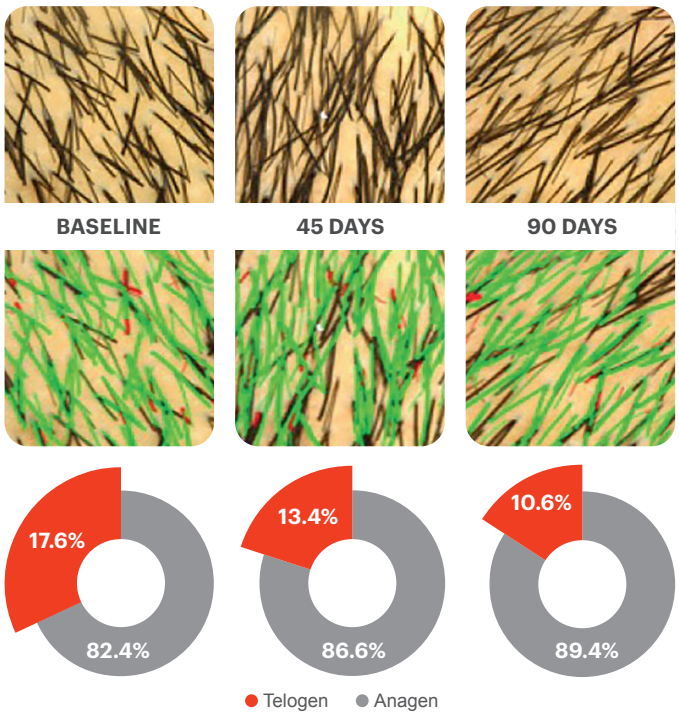


Figure 24. TrichoScan scalp images before treatment (baseline), after 45 and 90 days.

Case Report 6

Patient identification: M.A.N.
Gender: Male
Age: 27

Diagnosis
Androgenetic alopecia.

Treatment protocol
- TrichoOil™ (once per week)
- TrichoWash™ (daily)
- TrichoCond™ (daily)
- TrichoSol™ + Minoxidil 3.0% (daily)

Results
After 45 days and 90 days, an increase in anagen hair was observed. The use of minoxidil associated with **TrichoConcept™** protocol showed effectiveness, even when this active ingredient was prescribed in percentage and posology lower than usual (Figure 24).

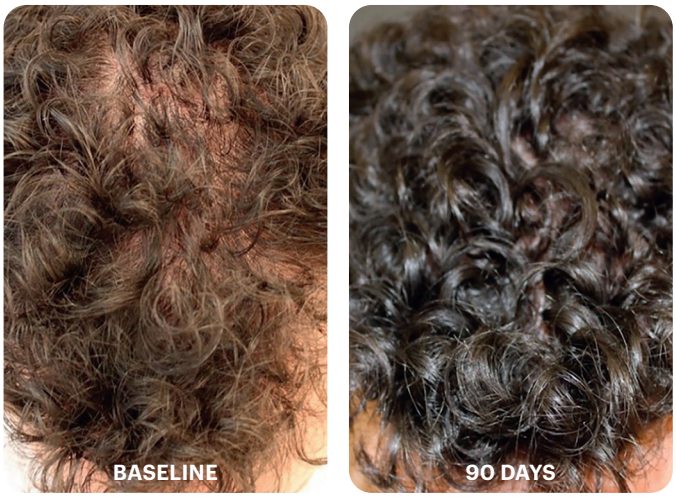


Figure 25. Hair shaft images before treatment (baseline), and after 90 days.

Case Report 7

Patient identification: J.P.M.
Gender: Male
Age: 43

Diagnosis
Androgenetic alopecia, seborrheic dermatitis.

Treatment protocol
- TrichoOil™ (once per week)
- TrichoWash™ (daily)
- TrichoCond™ (daily)
- TrichoSol™ + Minoxidil 5.0% (daily)

Results
After 90 days of treatment with the **TrichoConcept™** protocol, a significant improvement in the desquamation and new hair growth was observed (Figure 25).

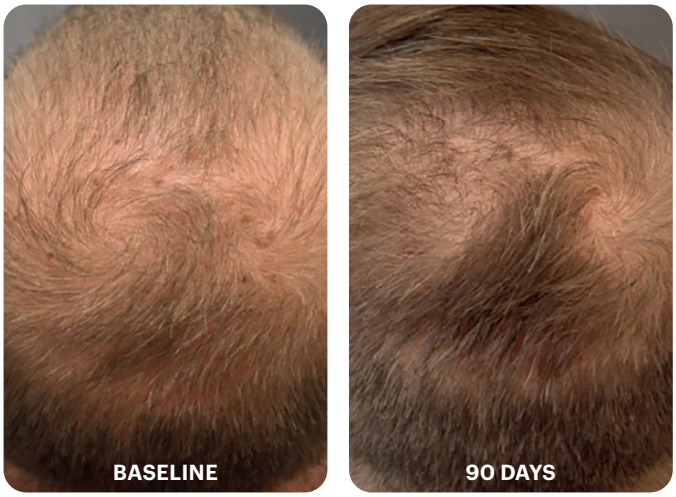


Figure 26. Hair shaft images before treatment (baseline), and after 90 days.

Case Report 8

Patient identification: R.S.F.
Gender: Male
Age: 28

Diagnosis
Androgenetic alopecia, seborrheic dermatitis, dry hair.

Treatment protocol
- TrichoOil™ (once per week)
- TrichoWash™ + Ciclopirox 1.5% (daily)
- TrichoCond™ + D-panthenol 0.5% + Niacinamide 0.5% (daily)
- TrichoFoam™ + Minoxidil 5.0% (daily)

Results
After 90 days of treatment with the **TrichoConcept™** protocol, a significant improvement in the rarefaction and growth of new hair was observed, with complete resolution of scalp discomfort. He also noticed smoother and shinier hair shaft (Figure 26).

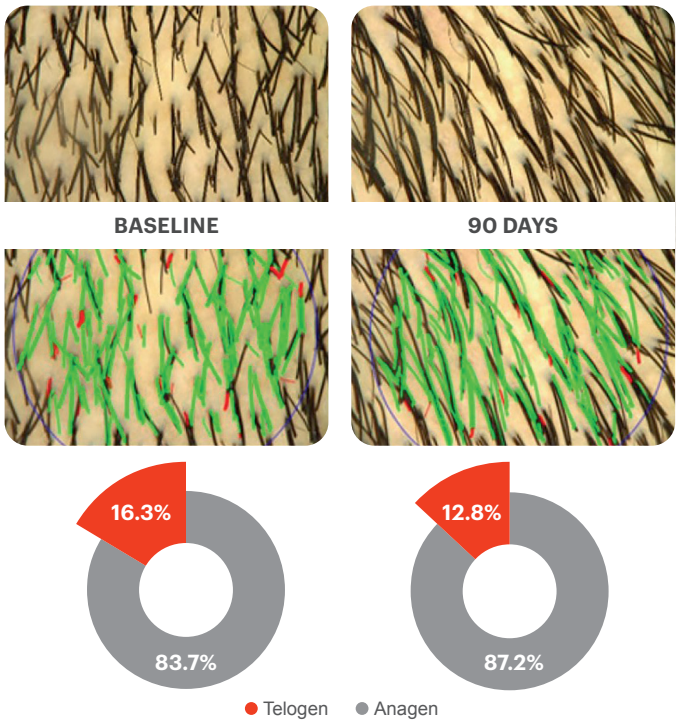


Figure 27. TrichoScan scalp images before treatment (baseline), and after 90 days.

Case Report 9

Patient identification: L.F.L.
Gender: Male
Age: 23

Diagnosis
Androgenetic alopecia, seborrheic dermatitis.

Treatment protocol
- TrichoOil™ (once per week)
- TrichoWash™ (daily)
- TrichoCond™ (daily)
- TrichoFoam™ + Minoxidil 3.0% (daily)

Results
After 45 days and 90 days, an increase in anagen hair was observed. The use of minoxidil associated with **TrichoConcept™** protocol showed effectiveness, even when this active ingredient was prescribed in percentage and posology lower than usual (Figure 27).

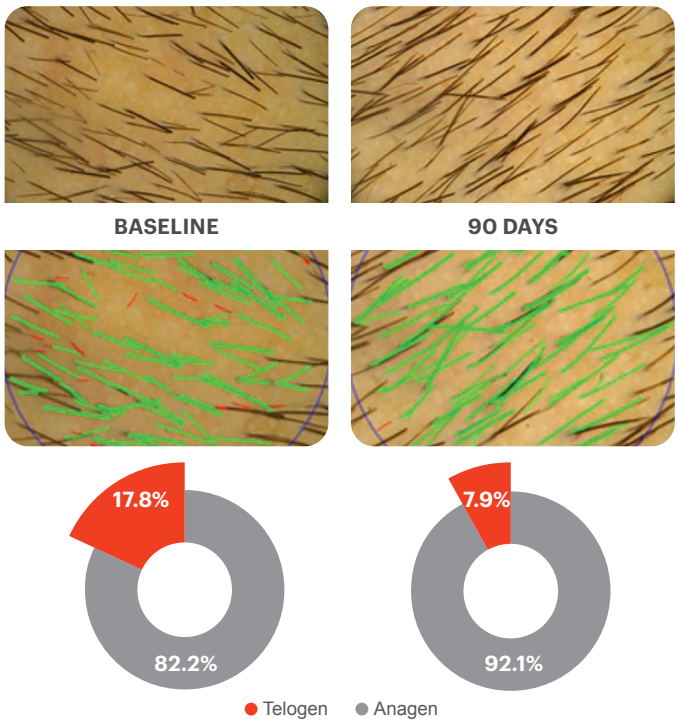


Figure 28. TrichoScan scalp images before treatment (baseline), and after 90 days.

Case Report 10

Patient identification: L.B.L.
Gender: Female
Age: 67

Diagnosis
Telogen effluvium, androgenetic alopecia.

Treatment protocol
- TrichoOil™ (once per week)
- TrichoWash™ (daily)
- TrichoCond™ (daily)
- TrichoFoam™ + Minoxidil 3.0% (daily)

Results
After 90 days, an increase of anagen hair was observed (Figure 28).

5.2. Stability of TrichoConcept™

According to the United States Pharmacopeia (USP)[67], in the absence of stability data, the beyond-use date of preserved aqueous formulations should be no later than 35 days, stored under refrigeration (2 to 8 ºC) or at room temperature (20 to 25 ºC), and protected from humidity.

The **TrichoConcept™** was developed to be compatible with the most commonly prescribed APIs used for alopecia treatment. A complete Formulary with the suggested formulations compounded with the **TrichoConcept™** and the Compatibility Table are available at Fagron.com.

5.3. Safety of TrichoConcept™

The safety of all vehicles from the **TrichoConcept™** line was evaluated in clinical studies to assess the skin's primary and accumulated irritation potential, skin sensitization, photoallergy and phototoxicity potential. The studies conditions were as follows:

- *Primary and accumulated skin irritation and sensitization (patch test):* the test was performed on human study subjects, male and female, age range from 18 to 69 years old, with skin phototype II to IV (Fitzpatrick). The frequency of application was established as 9 applications in the first 3 weeks (induction period), and 1 application in the last week (challenge period).
- *Photoallergy and Phototoxicity (patch test followed by ultraviolet irradiation):* the test was performed on human study subjects, male and female, age range from 20 to 70 years old, with skin phototype II to III (Fitzpatrick). The frequency of application was established as 6 applications in the first 3 weeks (induction period), and 1 application in the last week (challenge period). After 24 hours, the product was removed and, after 30 minutes, the area received ultraviolet irradiation.

After the completion of the studies, all the tested products:

- Do not induce primary and accumulated skin irritation
- Do not cause irritation
- Do not induce skin photoallergy or phototoxicity

TrichoConcept™ is formulated to be biocompatible with the hair and the scalp, without causing dryness or irritation. **TrichoConcept™** is free from allergens and controversial ingredients such as dyes, alcohol, parabens, mineral oils, sodium lauryl sulfate, propylene glycol, phthalates, silicones and petrolatum. **TrichoConcept™** vehicles have no safety concerns associated with any of their components and are cruelty-free, vegan, BSE/TSE-free (Bovine Spongiform Encephalopathy/ Transmissible Spongiform Encephalopathy), and GMO-free.

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