Identifying priority indications for APRILINE® dermal fillers based on clinical trials

The aesthetic cosmetology market offers a vast selection of dermal fillers based on hyaluronic acid, and estheticians rarely accept the remarkable properties of dermal fillers based on marketing material solely; they prefer evidence-based medicine. This is the reason why the histological and morphological research of tissue reaction to the administration of dermal fillers is in high demand. In addition to studying the product's safety, this research allows scientists to substantiate new efficient and advanced methods of using dermal fillers.

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INTRODUCTION

APRILINE® dermal fillers (Suisselle, Switzerland) are available in two forms: APRILINE® NORMAL and APRILINE® FORTE. These are monophasic, homogeneous, sterile apyrogenic gels with high plasticity. APRILINE® NORMAL contains biosynthetic hyaluronic acid modified in accordance with APRI technology (23 mg/ml) with 9% reticulation. APRILINE® FORTE has a higher (14%) HA reticulation.

The APRI process of modifying the spatial structure of HA molecules takes place due to the formation of efficient bilateral connections between the molecules of 1.4 butanediol diglycidyl ether (BDDE) with various macromolecular chains of HA in a highly concentrated environment. This process results in absolute and completely uniform molecular crosslinking free of BDDE residues. Furthermore, the crosslinking process is carried out without supplemental chemical agents, such as acids or bases, which ensures the safety of APRILINE® dermal fillers. The solution is then hydrated to the desired concentration of HA (23 mg/ml) and purified, providing the required product viscosity and reticulation. The viscoelastic properties of the gel fully correspond to the characteristics of the natural macromolecules in the extracellular matrix. Based on the product's properties and the peculiarities of its production, the above-mentioned product line has to have the highest affinity for the dermis, high safety, and sufficient ductility, matching the corresponding characteristics of the skin. Our clinical experience has completely confirmed these properties. APRILINE® perfectly fills the space between collagen and elastic fibers, and it fully integrates into the dermis. The product restores skin moisture, increases its elasticity and collagen synthesis, and decreases wrinkles. The maximum effect can be achieved in conditions of HA deficiency.

We carried out a study on the performance of APRILINE® in the bodies of laboratory animals by evaluating the process of product biodegradation in tissues after a single intradermal and subcutaneous injection. We also investigated the effect produced on the tissue based on long-term product usage.

STUDY DESIGN

The product was administered to outbred guinea pigs; these laboratory animals are more susceptible to various sensitizing factors compared to other species, and because guinea pigs have a thin and delicate skin, a small subcutaneous fat layer, and wide, flat bones, they make ideal subjects. The animals were divided into two administration groups:

1. APRILINE® NORMAL: introducing the filler intradermally and subcutaneously; and
2. APRILINE® FORTE: introducing the filler intradermally and subcutaneously. The monitoring of behavioral responses along with macroscopic and histological evaluation of the product's performance in the tissues was carried on the 3rd, 10th, 20th, 30th, 50th, and 90th day following product administration.

RESULTS

Intradermal product administration

A visual histological assessment following the administration of APRILINE® NORMAL intradermally on the 3rd, 10th, and 20th days (Fig. 1) reveals sections of soft granulation tissue containing a variety of cellular elements, which includes the administered substance.

The color and transparency of the substance has not changed. On the 30th and 50th days (Fig. 2) following product administration, the formation of trabecular connective structures is detected. A soft connective tissue consisting of spindle-shaped fibroblasts, thin collagen fibers, numerous thin-walled vessels, and the remaining gel not affected by resorption could be found between trabeculae.

On the 90th day (Fig. 3), the morphological pattern is a fully formed trabecular connective structure composed of fibrous cells with elements of angiogenesis and functional capillaries, among which there are areas of substance without any signs of condensation, decomposition, or resorption.

On the 3rd day following the administration of APRILINE® FORTE intradermally, the following effects can be observed: swelling and partial destructive changes in the administration areas; moderate leukocyte infiltration along with the destruction of cells and blood vessels in the mesh layer; and denaturation of the collagen matrix. A granulation tissue consisting of randomly arranged fusiform fibroblasts and thin, immature collagen fibers begins to form at this stage. This tissue contains numerous newly formed vessels and a moderate number of inflammatory infiltrate cells. On the 10th and 20th days (Fig. 5), the histology pattern shows a newly formed connective tissue containing a significant number of cells (primarily fibroblasts). In addition, blood vessels and collagen fibers accompanied by the formation of a fibroblast-collagen gel structure around gel droplets can be noted. On the 30th and 50th days (Fig. 6), a fully

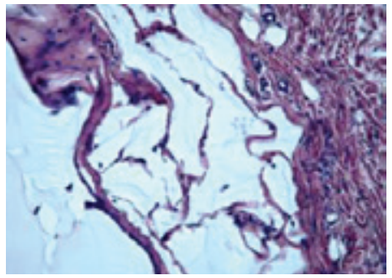

Figure 1.
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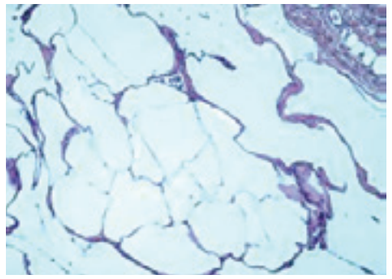

Figure 2.
Histology on the 30th day following the intradermal administration of APRILINE® NORMAL.

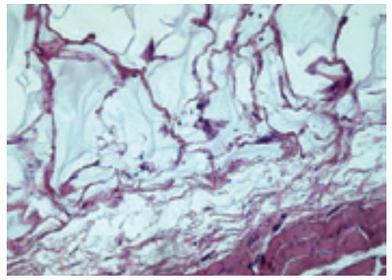

Figure 3.
Histology on the 90th day following the intradermal administration of APRILINE® NORMAL.

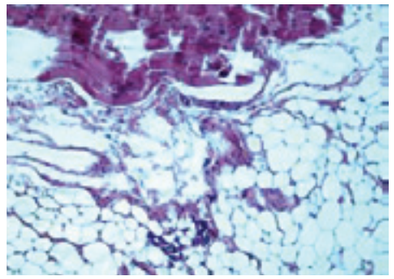

Figure 4.
Histology on the 3rd day following intradermal administration of APRILINE® FORTE.

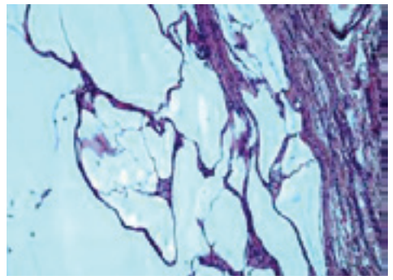

Figure 5.
Histology on the 10th day following the intradermal administration of APRILINE® FORTE.

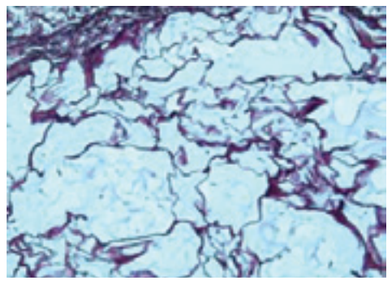

Figure 6.
Histology on the 30th day following the intradermal administration of APRILINE® FORTE.

formed fibroblast structure can be observed. Some gel with almost no resorption appears within the structure. Neither cellular response nor infiltration of inflammatory cells occurs. On the 90th day of the study, one can observe a fully formed intradermal structure consisting of fibrous particles with elements of angiogenesis and functional capillaries, among which one can locate areas of gel with no signs of condensation, decomposition, or resorption.

The proliferation of fibroblastic cells is not observed at this stage. The formation of blood vessels, especially the endothelium, is more evident. There is no infiltration by inflammatory cells.

Based on the described histology, we confirm the uniform distribution of the gel in the intercellular space, slow biodegradation, and a gradual and uniform replacement of the gel by the soft connective tissue without the formation of a capsule. The latter suggests that intradermal administration of APRILINE® NORMAL and APRILINE® FORTE dermal fillers provide stable, natural results without the risk of overcorrection (Fig. 7).

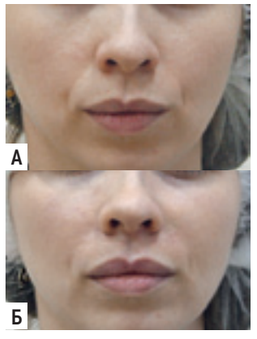

Figure 7.
The result of the nasolabial folds correction with APRILINE® FORTE dermal filler.
A. Before **B.** After.

Subcutaneous product administration

When APRILINE® FORTE is administered subcutaneously, the microscopic observation resembled the previous one—on the 3rd day (Fig. 9), there was an interstitial edema and a moderate polymorpho-cellular infiltration with the predominance of the lymphocytic-histiocytic cells, which completely regressed by the 10th day and has not appeared afterwards. Starting from the 10th day, the formation of connective tissue around the gel structure with the chaotic arrangement of cells and fibers takes place. During further observation, the cells and connective tissues arrange more densely. Starting from the 30th day (Fig. 10), a trabecular-lacunar structure is formed. Soft connective tissues and any substance not affected by resorption appear between trabeculae till the 90th day of the observation (Fig. 11).

If the product is administrated subcutaneously, the use of APRILINE® NORMAL and APRILINE® FORTE for achieving a lining-effect is completely justified due to the uniform gel distribution and subsequent formation of trabecular structure in the surficial hypodermis.

CONCLUSION

The study found that none of the administration methods had a toxic, sensitizing, or local irritating effect on the surrounding tissue. The gel appears within the trabecular lacunar system till the end of product administration (90 days) with no signs of morphological changes. The latter is formed within this timeframe with the administration of APRILINE® FORTE and at a later stage with the administration of APRILINE® NORMAL. Laboratory animals demonstrated normal behavioral reactions and normal temperature and body weight parameters throughout the entire experiment. Based on the research, we may conclude the following:

Figure 8. The result of correcting the shape and volume of the lips with APRILINE® NORMAL dermal filler. **A.** Before. **B.** After.

APRILINE® NORMAL has proven its efficiency in achieving the effect of natural lips. Due to the uniform distribution of the gel, administration of the product to the red area of the lips results in improved micro-relief; the lips appear as saturated, and moisturized. Any lipstick easily glides over the lips without concentrating in the folds (Fig. 8).

• APRILINE® dermal fillers are safe and can be used for aesthetic correction of the skin (as of the 10th day, there are no signs of inflammation, and no connective tissue capsule is formed);
• There is no overcorrection risk (the product is distributed uniformly with either intradermal or subcutaneous administration);
• The deficit of tissue is compensated for in a natural way (with the newly formed connective tissue); and
• The product demonstrates a lasting effect. (This research was done on guinea pigs; however, considering their lifespan in comparison to humans', researchers conclude that the analyzed substances tend to remain in human tissues for more than one year).

In conclusion, it should be mentioned that the study of the product performance in the tissue allows one to precisely choose the appropriate indications for the procedure, making it as efficient as possible.

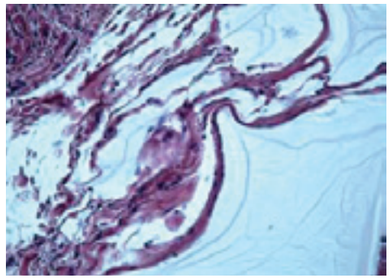

Figure 9.
Histology on the third day following the subcutaneous administration of APRILINE® FORTE.

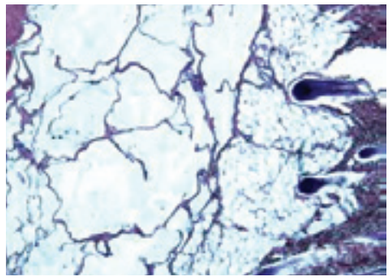

Figure 10.
Histology on the 30th day following the subcutaneous administration of APRILINE® FORTE.

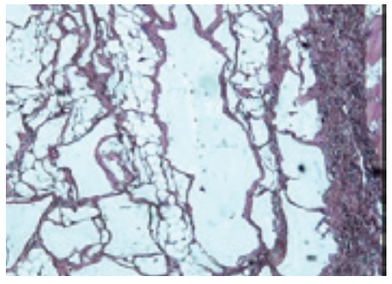

Figure 11.
Histology on the 90th day following the subcutaneous administration of APRILINE® FORTE.

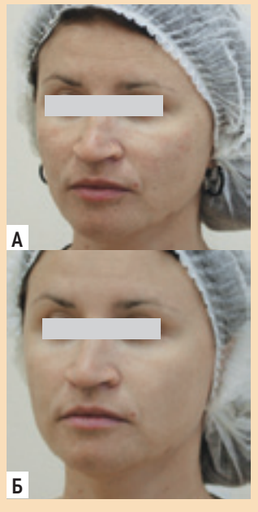

Figure 12.
Lining-effects in patients with the «tired» aging morphotype.
A. Prior. **B.** After.

* Lining-effect is a smoothing of superficialtissues and filling the missing volume via uniform distribution of the administered gel within soft tissues. Subsequent replacement of the gel by connective tissue provides mechanical strengthening of the dermis and hypodermis, reducing their displaceability relative to each other, and allows the subject to maintain the results for 6–8 months. Therefore, when the product is administered subcutaneously with a cannula, one can achieve long-term lifting and firming of soft tissue associated with «tired» aging morphotypes (Fig. 12). In addition, the product provides wrinkle reduction and relieves issues associated with the fine-wrinkled type of aging (Fig. 13). This procedure is particularly relevant in «sensitive» areas, such as the forehead, cheeks, and decollete (Fig. 14). The result is visible immediately after the procedure and gradually becomes more evident during the following 13–20 days.

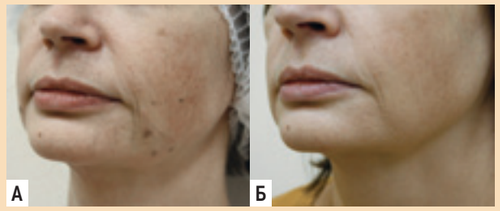

Figure 13.
Lining-effects in patients with the finely-wrinkled aging morphotype.
A. Prior. **B.** After.

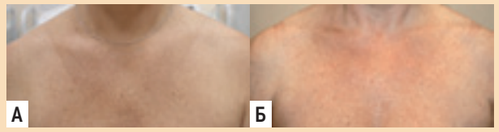

Figure 14.
Lining-effect in the upper chest.
A. Prior. **B.** After.