Dermotological Diseases and Human Placental Extracts Psoriasis Case Study in Europe

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Abstract:

Introduction: Placenta is the source of a large number of biologically active molecules, Benefits: Wound healing and tissue repair, antioxidant, inducing melanogenesis [1,2], immunoregulatory effect[3], and rejuvenation procedures.[4]
Methods: Patients treated for 12 weeks, with the following selection criteria
Main variable to value: Percentage of patients to response to the treatment with two criteria:a) Global clinic evaluation by the doctor: "practically clean" or "clean".
b) Number of patients whose the Superficial Index and Severity of Psoriasis (PASI) improve in more than 75% over the basal status (PASI>75%).
Results: In the preliminary results look great hydration of psoriasis plaques, leaving the clean area by 50% in the first two weeks of treatment and gradually improved. In photoaging, it was found that with mesotherapy sessions each week during the first month and continue with a monthly session, the wrinkles are smoothed, appearance of the skin is hydrated, soft and bleached.
Discussion: We have tested placental extracts in psoriatic patients considering placental extract could improve the patient status due to the improvement of water retention capacity of the skin cells. It remains to establish the appropriate maintenance dose to prevent or ameliorate exacerbations in patients with psoriasis. In patients with photoaged skin pose cycles of 4 weekly treatments 2 times a year and a monthly maintenance. Side effects have not appeared in any case.

INTRODUCTION

Placenta is the source of a large number of biologically active molecules, hepatocyte growth factor (HGF), epidermal growth factor (EGF), transforming growth factor _ (TGF_) and transforming growth factor _ (TGF-_), and others such as vitamins, minerals, aminoacids, glucopolysacharides, **…)**[5]

Hormone age is a key evidence for aging and IGF1 (Insuline-like Growth Factor 1) is the most important marker of hormone age[5]. Benefits: Wound healing and tissue repair, antioxidant, inducing melanogenesis, immunoregulatory effect, and rejuvenation procedures**.**[6,7,8]

We have made this pilot study "**12 weeks study to evaluate the evolution of adult patients diagnosed with psoriasis in moderate to serious plaques after the Laennec® use**". With a collaboration of the Spanish and Swiss doctors and under the managing of the Doctor Llorca. It's a multicentric study with 24 cases and it is still open.
Abbreviations: BSA Body Surface Affectance, **PASI** Index of Severity and Psoriasis Area and **PGA** Global clinical assessment of Psoriasis

OBJECTIVES

Primary objectives:

- a) Establish the percentage of responders under this treatment , after using it for 12 weeks
- b) Establish **time** for the treatment's reaction.

Secondary objectives:

- a) A record of the **adverse effects**
- b) The number of the medication's administration until a **therapeutic response** is reached

Furthermore, we note for the first time a response to Laennec ® with intramuscular administration in Psoriasis cases

JUSTIFICATION

We know that psoriasis is a cronic inflamatory illness[9] characterized by erythematosus plaques, with clear borders. It is more frequent on limbs and scalp [10,11]. It has two components: an epidermal hyperproliferation and a swelling on the dermis[12]
Diagnosis is clinical. It does not need any histological checkings. We do not have any specific analysis [13]
We know that **psoriasis** is a **genetical disorder** (there is a mutation in the PSORS-1's genoma, in the chromosome ·6), with a strong influence of **enviromental factors**.
It is an **autoimmune illness**, with an immune cellular system activation. It is an immunepathogenetic process mediated by T lymphocytes[14]

This affects a 1-3% of the European population and has a strong impact on the life's quality: pain, itching, psicological problems.[15]...
The most frequent way is a psoriasis with plaques
Today's treatments have a **potentially serious toxicity**, as hepatoxicity, nephrotoxicity, bone marrow depression, neoplasias. [16,17]. Furthermore, these are doses without a security in the treatment's duration [18]. We need a treatment for psoriasis that has guarantees to be safe and efficient in the long-term. Now we have some alternatives as the biological agents, that are efficient, but they have some risks of malignancy and infection [19].
Our main **working hypothese** is evaluating the **human placenta extracts as a safe and efficient treatment on psoriasis.**
We have got many clinical and experimental researches with several treatments for psoriasis. BSA and PASI are the most usual scale to measure the results.
But if we search on PubMed for some researches on the psoriasis treatments with placenta extracts we only find four studies that link psoriasis to topical treatment and none of these extracts of human placentas are considered as a systemic treatment.
[20,21,21,23]

Maybe the most researched medication is STELARA. A monoclonal antibody therapy, with the Phoneix-1, Phoenix-2 and Accept trials in the long term.[24 25]

PILOT STUDY DESIGN

This **Pilot Study** Design is: a **multicentric study** with a **12 weeks** duration of active treatment. This study's population have been **24 patients**, but it is still open. The form of administration and posology: **2 intramuscular injections**, twice a week for 12 weeks.
In the **visit "zero"** a first evaluation is done and the patient is properly informed. A study and classification is done. Likewise, the patients sign to consent informed that they agree to participate and they do not have any problems that pictures of them are taken and that they will follow the treatment.
After this every visit is evaluated for the next 12 weeks. At the end of the treatment, we wait for 2 weeks and a final evaluation is done at the 13rd visit.

The trademark is **Laennec inj**, ® injection. The composition is 112 mgs of a water-soluble substance of an enzymatic human placenta product.

Design - Development and evaluation

Evaluation criteria.

We have used a **PASI**, **PDI** and **PGA** scale and the adverse events. The main evaluation variables are these two: firstly, **a global clinical evaluation by the researcher** where patients are considered as **"virtually clean"** and **"clean".** Secondly, the patients whose **PASI improves over a 75%** on the baseline. This lets us establish the percentage's responder according to the **EMA** (European Medicines Agency). Furthermore, we have introduced some more variables (PDI, etc.)

Design- development

Zero Visit (selection): Explanation/CI, criteria for inclusion/exclusion. Features: sex, race, weight (kg), size (cm), smokers, Date of the Psoriasis Diagnose, health record, previous medication
Visits 1-12: Researcher's evaluation. Adverse events with no evaluation. Pictures of visits 1 and 4
Visit 13 (2 weeks after the end). Researcher's evaluation and pictures

Researcher's evaluation
Visual evaluation of representative injuries. Index (≥). Body surface affected area (PASI scoring). Clinical global evaluation. PASI scoring
The researcher will evaluate according to the PASI scale the two most important injuries

Design- selection
In order to include a patient in this research we need that they fully meet the requirements, otherwise they are not included. Patients can be of both genders, between 18 to 65 years, with a psoriasis diagonse with moderate to severe plaques, a negative pregnancy test and they should not follow any hormonal treatment

Our researches has been done with 24 patients and it is still open. There are 8 men and 16 women. The ages are: 1 patient: 20-30 years old, 5 patients: 31-40 years, 10 patients: 41-50 years and 8 patients: 51-60 years old

Psoriasis Seriousness Evaluation

Psoriasis: slight to moderate: Good control of damages only with external treatments. BSA>10% or PASI 10 or higher

Moderate Psoriasis: It is still possible to control the illness with external treatments. BSA>10% or PASI 10 or higher.
Moderate to serious psoriasis: External treatments cannot be control the illness. BSA>10% or PASI 10-20
Serious psoriasis: It needs a systemic treatment to control the illness. BSA>20% or PASI>20

Estimates of the global clinical evaluation of psoriasis for doctors (PGA) for the whole body

For the global clinical psoriasis evaluation on the body, the PGA scale is used, and the "virtually clean" or "clean" criteria are included**.**

- **Serious**: rise of the skin plaque, desquamation and erythema
- **Moderate to serious**: rise of the skin plaque, desquamation and erythema
- **Moderate**: moderate rise of the skin plaque, desquamation and erythema
- **Slight**: slight rise of the skin plaque, desquamation and erythema
- **Virtually clean**: from slight to clean
- **clean**: without rests of psoriasis (sometimes, it is possible to find a little post-inflammatory hyperpigmentation)

Clinical psoriasis

There are several forms of psoriasis and these can coexist.

- With erythema-scaly plaques,
- drops,
- inverted,
- psoriasic erythrodermia,
- localized pustular form,
- a spread pustular form,
- an active psoriasis induced by medication, and the medication's name is recorded.

Estimates of the index surface and severity of psoriasis

PASI is a surface index and the psoriasis seriousness. It has a scoring from 1 to 4 according to the seriousness, and from 1 to 6, depending on the affected skin surface. It's an **evaluation system** of the psoriasic damages and the patient's answer to treatments. It represents a rate from **0 to 72.** This organism can be divided in **4 regions**: head (c=), upper limbs (s), axio-appendicular (t) and legs (i), which represent a 10%, 20%, 30% and 40% of the body surface. Neck is here considered as a part of head. Axillas and groin are here considered as part of the axio-appendicular surface and nates are considered as a part of the legs. All of these parts of the body are evaluated separatedly according to the seriousness of the injuries depending on the **erythemas (E), the infiltration (I) and desquamation (D), in a scale from 0 to 4.** [26]

PSORIASIS DISABILITY INDEX (PDI) (spanixh; Vanaclocha y cols, 2005)

PDI is a **disability index** of psoriasis. It is a questionnaire with 15 items that the patient must answer . It consists of **15 items** divided in five dimensions: activities for everyday

(5 items), work/researches (3 items), personal relations (2 items), leisure (4 items) and treatment (1 item). The reaction goes from 0 (psoriasis interference) to 3 (maximal psoriasis interference) and a total rate from 0 to 45 (the higher the rate, the bigger the impact on the **life's quality**)

Psoriasis treatment

Topical therapy	**Fototherapy**	**Systematic therapy**
Topical corticoids Combined or isolated Inner injuries	Fotochemical therapy PUVA Fototherapy UVB Fototherapy UVA1	Metotrexate Ciclosporine Acitretin Fumarate* *It is only available in Europe
Calcipotriol Tazarothene tar dithranol	Combined therapy	**Biological agents** Alefacept Efalizumab Etanercept Infliximab Adalimumab

Modificado de Yamauchi PS, Rizk D, Kormeili T, Patnaik R, Lowe NJ. Current systemic. Therapies for psoriasis when are we know. J Am Acad Dermatol. 2003: 49:S66-67[27]

Working hypotheses: to analyze the human placenta's extracts on psoriasis, as a safe, effective and convenient treatment "ideal treatment"

Our working hypotheses is to analyze the human placenta's extracts on psoriasis, as a safe, effective and convenient treatment
Medical effectiveness: Curative. Specific action on the psoriasis pathogenesis. Quick clinical reactions. Constant control of the illness with long-term drugs. Effective as monotherapy. Effective as associated illness
Security. Safe as a chronic treatment and limited use . Maximal control. Suitable for all ages and population groups. Minimal medical interaction. Minimal contra-indication
Convenience. Convenient and well accepted by patients. Easy application

MECHANISM OF ACTION OF HUMAN PLACENTAL EXTRACTS (LAENNEC INJ)

HPE (human placental extracts) is the only component of Laennec inj. Several are the properties associated to the mechanism of action of this active ingredient in relation to the skin functionality. This is a summary of scientific publications:

Hypersensitivity

-Reduce the number of CD4(+) T cells in peripheral blood. Decrease peripheral production of Th2-Type cytokines in Ag-challenged site by the cyclo-trans-4-L-hydroxyproplyl-L-serine[28]

-Reduce lymphocyte infiltration.Decrease of tissue infiltrating lymphocytes[29]

-Protective effect associated with down-regulation of serum IgE level and inflammatory cytokine production (IL-1_, IFN-γ, TNF_, IL-4 and IL-17) in total lymph node cells and CD4(+) cells.[30]

Immunomodulating Activity

-Decrease of initially high levels of neutrophils[31,32]

-Decrease the level of eosinophil s, serum IgE, serum cryoglobulines, number of monocytes, titre of R-protein and the number of mediomolecular peptides[33,34]

Wound Healing and Tissue Repair[35,36]

-Increase of fibroblast proliferation[37]

- Increase of the content of fibronectine type III line peptide (responsible of curing process)[38]

-Contents glutamate which induces chemotasis of neutrophils accompanied by polarization of the actin cytoskeleton and by polymerization of F-actin

-Promotes cell adhesion[39]

- Increase of TGF-_ in the early stage of wound healing and VEGF in the late phase[40]

- Free and bound NADPH in HPE is a potent wound healer and it's the substitute of the glutathione reductase[41]

Moisturizing

Increase water retention of the epidermal cells[42]

Antioxidant

Glycine (g)-XY aminoacid (derived from collagen) is an antioxidant component of HPE[43].

L-Tryptophan, an aminoacid on HPE, suppress the lipid peroxidation in the oxidative stress[44]

For a clearer exhibition of the results, we have chosen the "typical" patient. She is a selected patient with a the most spread psoriasis and, furthermore, several types of psoriasis. We will need know to work with the patient on the process to the healing

4 FOTOS

CONCLUSIONS

- In an 80% of patients the primary objective of this research has been reached. Signs and symptoms of the evaluated psoriasis cases have been reduced. We have followed the PASI scale (PASI-75) after twelve treatment weeks.

- Reached results with two blisters of LAENNEC ® (112 mgs/blister), twice a week/12 weeks.

- We have noticed a 75% healing from third to sixth week. This kept like this until the end of our treatment

- The reached results were after a medical evaluation two weeks after the end of the treatment

- We have noticed that the plaques can come back on the elbows in a patient after a stress time, but not on the rest of her body surfaces

- There is only a patient who did not improve with regard to the beginning of the treatment. However he has some differences with the rest of the patients: he is a social drinker and takes sintrom (acenocumarol)
- We have not noticed any adverse symptoms
- A weekly INR was asked to the patient with sintrom. We have not noticed any disturbances associated with Laennec ®
- As a collateral effect we have noticed an hypopigmentation in the clean plaque
- As a positive collateral effect we have noticed an improvement in the quality of the skin on the body and especially on the face and even a kind of antiaging effect
- We have noticed a 100% healing from thorax, abdomen, back and scalp in all patients
- The human placentas extracts of Laennec ® of JBP can be a good help on psoriasis patients in plaques in a systematic way; it improves the damages and prevents negative side effects or also more treatments
- We need to establish the way we track the results after a short or a long time after the treatment

BIBLIOGRAPHY

1. Singh SK and cols. Human placental lipid induces melanogenesis through p38 MAPK in B16F10 mouse melanoma. Pigment Cell Res 2005 Apr; 18 (2): 113-21
2. Saha B and cols. Transcriptional activation of tyrosinase gene by human placental sphingolipid. Glycoconj J. 2006 May; 23 (3-4): 259-68
3. Lee YK, Chung HH, Kang SB. Efficacy and safety of human placental extract in alleviating climateric symptoms: prospective, randomized, double-blind, p placebo-controlated trial. J.Obstet Gynaecol Res. 2009 Dec; 35(6): 1096-101
4. Kong M y Park SB. Effect of human placental extract on health status in elderly knoreans. Evidence-Based Complementary and Alternative Medicine Volume 2012 (2012), Article ID 732915, 5 pages doi: 10.1155/2012/732915
5, Marleau AM and cols. Reduction of tumorigenicity by placental extracts. Anticancer Res, 2012 Apr: 32 (4): 1153-61
6. Taniguchi T and cols. Increase in the circulating level of hepatocyte growth factor in gastric cancer patients. Br. J. Cancer 1997: 75(5): 673-7
7. Schomber T and cols. Placental growth factor-1 attenuates vascular endothelial growth factor-A-dependent tumor angiogenesis during beta cell carcinogenesis. Cancer Res. 2007 Nov 15; 67 (22): 10840-8
8. Kemik O and cols. Preoperative serum placenta growth factor level as a new marker for stage II or III colorectal cancer patients. Turk J Gastroenterolo. 2012 Apr; 23 (2): 104-9
9. Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC. Health Technol Assess 2000; 4(40)
10. *Lázaro Ochaita P, Suárez Fernández R. Inf Ter Sist Nac Salud. 2001;25(4):105-110*
11. *Menter A, Griffiths EM. Current and future management of psoriasis. Lancet. 2007;370:272-84.*
12. Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature. 2007, 445:866-73.
13. Krueger, G., Ellis, C. N. (2005) Psoriasis – recent advances in understanding its pathogenesis and treatment. J. Am. Acad. Dermatol. 53, S94-100.

14. Schön MP, Boehncke WH (2005). Psoriasis New England Journal of Medicine 352: 1899-1912.
15. Rapp SR, Feldman SR, Exum ML et al. J Am Acad Dermatol 1999; 41: 401-407.
16. Menter, A, Griffiths EM, Current and future management of psoriasis. Lancet. 2007; 370: 272: 84
17. Stern RS, Laived N, Melsky J, Parrish JA, Fitzpatrick TB, Bleich HL. Cuta-neous squamous-cell carcinoma in patients treated with PUVA. N Engl J Med 1984; 310:1156-61.
18. Lever LR, Farr PM. Skin cancer or premalignant lesions occur in half on high-dose PUVA patients Br. J Dermatol 1994; 131:215-9.
19 Ellis CN, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. N Engl J Med 2001; 345: 248-255.
20. Lodi A, Cattaneo M, Betti R, Marmini A, Masnada MC. G Ital Dermatol Venereol. 1986 Jan-Feb;121(1):XV-XVII. Local therapy of psoriasis with placental extracts
21. Novikova ZI. Vestn Dermatol Venerol. 1985 Oct;(10):46-8. Effect of placenta suspenson on the inmunologic indicators and dynamics of skin changes in patients with palmar and plantal pustulousus psoriasis
22. Vasil'eva LL, Amirova IA. Vestn Dermatol Venerol. 1984 Oct;(10):6-8. In vitro system for determining the use of inmunecorrective agents in patients with disseminated psoriasis
23. Hadida E, Sayag J, Tramier G, Valette P. Bull Soc Fr Dermatol Syphiligr. 1969;76(2):195-7. Pustulous and erythrodermal psoriasis
24. Smith CH, Anstey AV, Barker JN, Burden AD, et al. British Association of Dermatologists´ Guidelines for Biologic Interventions for Psoriasis 2009. Br J Dermatol. 2009; 161: 987-1019
25. CHMP Assessment Report for STELARA. Procedure No. EMEA/H/C/000958 Doc Ref. EMEA/CHMP/29255/2009. LINK
http://www.ema.europa.eu/humandocs/PDFs/EPAR/stelara/H-958-en6.pdf
26. Henseler T, Scmitt-Rau K. Comparison of BSA, PASI, and SAPASI PLASI as indices of severity and treatment response in patients with psoriasis.
In t J Dermatol 2008;47:1019-23.
27. Yamauchi PS, Rizk D, Kormeili T, Patnaik R, Lowe NJ.
Current systemic. Therapies for psoriasis when are we know.
J Am Acad Dermatol. 2003: 49:S66-67
28. Kim YS y cols. Preventive and therapeutic potential of placental extract in contact hypersensitivity. Int. Immunopharmacol. 2010 Oct. 10 (10): 1177-84. Epub 2010 Jul 7
29 Jingjing W y cols. Laennec protects murine from concanavalin A-induced liver injury through inhibition of inflammatory reactions and hepatocyte apoptosis. Biological and Pharmaceutical Bulletin Vol. 31 (2008) No. 11 P 2040-2044
30. Jash A. Kwon HK, Sahoo A, Lee CG, So JS, Kim J, Oh YK, Kim YB, Im SH. Topical application of porcine placenta extract inhibits the progression of experimental contact hypersensitivity J. Ethnopharmacol 2011. Jan 27; 133(2): 654-62. Epub 2010 Oct.30
31. Gupta R and Chattopadhyay D. Glutamate is the chemotaxis inducing factor in placental extract. Amino Acids 2009. Ju: 37 (2): 359-66. Epub 2008 Aug 23.
32. Schomber T and cols. Placental growth factor-1 attenuates vascular endothelial growth factor-A-dependent tumor angiogenesis during beta cell carcinogenesis. Cancer Res. 2007. Nov. 15:67 (22): 10840-8.
33. Tiwary SK y cols. Effect of Placental Extract gel and cream on non-healing wounds. J. Wound Care 2006, Jul: 15 (7): 325-8.

34. Yeam MJ. Therapeutic effects of Hominis placenta injection into an acupuncture point on the inflammatory responses in subchondral bone region of adjuvant-induced polyarthritic rat. (2003) . Biol Pharm Bull Oct 26 (10); 1472-7
35. Chakraborty PD y cols. In vitro induction of nitric oxide by mouse peritoneal macrophages treated with human placental extract. Int. Immunopharmacol, 2006 Jan: 6(1): 100-7, Epub 2005 Sep. 8
36. Chandanwale A., Langade D, Mohod V, Sinha S, Ramteke A, Bakhshi GD, Motwani M.. Comparative evaluation of human placental extract for its healing potential in surgical wounds after orthopaedic surgery: an open; randomized, comparative study. J. Indian Med Assoc. 2008 Jun; 106 (6): 405-8
37. Cho HR y cols. The effects of placental extract on fibroblast proliferation. J.Cosmet Sci. 2008 May-Jun: 59 (3) 195-202.
38. Chakraborty PD y Bhatacharyya D. Isolation of fibronectin type III like peptide from human placental extract used as wound healer. J. Chromatogr B Analyt Technol Biomed Life Sci. 2005 Apr 15: 818 (1): 67-73.
39. Nath S y Bhttacharyya D. Cell adhesion by aqueous extract of human placenta used as wound healer. Indian J. Exp. Biol. 2007 Aug; 45 (8): 732-8
40.Hong JW, Lee WJ, Hahn SB, Kim BJ, Lew DH. The effect of human placenta extract in a wound healing model Ann. Plast Surg 2010 Jul: 65(1): 96-100
41.De D, Chakraborty PD, Bhattacharyya D. Analysis of free and bound NADPH in aqueous extract of human placenta used as wound healer. J Chromatogr B Analyt Technol Biomed Life Sci. 2009. Aug 15; 877 (24): 2435-42. Epub 2009 May 15
42. Wu Z y cols. Molecular indentification an dexpression analysis of filaggrin-2, a member of the S100 fused-typed protein family. PloS One 2009, 4 (4): e5227. Epub 2009. Apr.22
43. Togashi S, y cols. Antioxidative collagen-derived peptides in human-placenta extract. Placenta. 2002. Jul; 23 (6): 497:502
44. Watanabe S y cols. L-tryptophan as an antioxidant in human placenta extract. J. Nutr. Sci. Vitaminol. 2002. Feb; 48 (1): 36-9