ACTA MEDICA TRANSILVANICA September;25(3):18-21
DOI: 10.2478/amtsb-2020-0042
Online ISSN 2285-7079

TOPICAL MAINTENANCE TREATMENTS IN CHRONIC DERMATITIS

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Keywords: *chronic dermatitis, treatment, side effects*

Abstract: *The epidemiological importance of chronic dermatitis is constantly growing, this pathology being more and more common regardless of age, in most countries of the world. The pathogenesis of chronic dermatitis is complex and involves aeroallergens, immunological, dietary, climatic and psychosomatic factors. Due to the frequent recurrences but also the side effects of allopathic medicines, the number of patients with chronic dermatitis who opt for alternative treatments is increasing. In this paper we have identified allopathic topical treatments versus alternative topical treatments used in chronic dermatitis for which there is scientific evidence. The PubMed and Research Gate databases were analysed, the analysed period being 2007 – 2019. The search criteria were "chronic dermatitis", "atopic dermatitis", "psoriasis", "alternative treatments", "natural treatments", "complementary treatments"," treatments for chronic dermatitis". We also analysed the mechanisms of action of drugs or active substances used as well as side effects secondary to allopathic and alternative therapies. New treatment options in atopic dermatitis, currently under evaluation, are topical inhibitors of phosphodiesterase and Janus kinase. For patients with chronic dermatitis who want alternative therapies to allopathic ones, there are products based on oat (Rhealba variety), camphor leaves, hydroxytyrosol, enzymatically interstered fats etc.*

INTRODUCTION

The most commonly known chronic inflammatory disease is atopic dermatitis (AD). This condition can progress from mild to severe forms, with risk of complications. It is most common among children (up to 25%) and rarer among adults (2-3%) in the majority of countries around the world, with a high prevalence in the developed countries.(1,2) Clinically, AD is characterized by erythematous-squamous lesions, intensely itchy, sometimes with exudation and the possibility of superinfection. These aspects greatly affect the quality of life of the child with AD but also of the parents. The AD etiopathogenesis is complex. The involved factors are multiple: genetic factors (filaggrin genes), skin barrier defects (3), psychosocial factors, infections, and some foods, aeroallergens, climate changes, and immunological factors.(4) The choice of allopathic or alternative therapy for the treatment of chronic dermatitis (CD) should be made after confirmation of the diagnosis and taking into account the following factors: causes of its occurrence, age, sex of patients, anamnestic details, drug treatments administered before diagnosis, informing the patient about side effects of some therapies (ex. skin atrophy after prolonged use of topical dermatocorticoids). Also, the choice of therapeutic method must be made according to the psychosomatic factors specific to each individual.

Regardless of the people, traditional medicine had its followers, more or less trained in terms of pharmacology and toxicology, respectively. Depending on the alternative therapy applied, long-term consumption of herbs can lead to a number of side effects (5) or interactions between drugs and herbs, or between herbs and foods, with adverse effects on the health of the individual.

In chronic dermatitis, there can be used topical anti-inflammatory and/or immunomodulatory therapies in combination with emollients, moisturizers and special shower gels for cleansing the skin and alternative topical therapies. These will maintain the integrity of skin barrier, respectively the physiological hydro-lipid layer of the skin.(1,6-11) In the treatment of chronic dermatitis among the alternative methods for which there is scientific evidence we list: phytotherapeutic complex - PTQX (1), biological extract of Aquaphilus dolomiae (12) with anti-inflammatory and immunomodulatory action, organic oat plant extract Rhealba variety without protein, protected by three patents of international inventions (WO2010 / 054879A2, WO2010/054878 and FR2938439) (6), green tea (13), enzyme-mediated fat preparation (14), tetramethoxyluteoline (9), eupatiline (10) etc.

Currently, in chronic dermatitis, it is taken into account that during exacerbations, topical therapies have a local anti-inflammatory action through the use of dermatocorticoids, calcineurin inhibitors and glutathione synthesis derivatives. During calm periods of dermatitis, the use of emollient creams and gentle washing gels with moisturizing effect is insisted on.

Also, by analysing personal and family history, individual factors (age, type of lesions, affected body areas) and identified etiological factors, personalized therapeutic schemes can be achieved, much more effective. New promising treatment options in atopic dermatitis are topical inhibitors of phosphodiesterase and Janus kinase.

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Article received on 18.06.2019 and accepted for publication on 10.08.2020

Our paper summarizes the treatment alternatives nowadays and the new perspectives of topical therapy in CD, with a focus on AD.

MATERIALS AND METHODS

To identify allopathic topical treatments versus alternative topical treatments for which there is scientific evidence, we analysed the PubMed and Research Gate databases, the period analysed being 2007 - 2019. The search words were "chronic dermatitis", "atopic dermatitis", "alternative treatments", "natural treatments", "complementary treatments", "treatments for chronic dermatitis". We also analysed the mechanisms of action of these treatments.

RESULTS AND DISCUSSIONS

Allopathic topical treatments currently applied in chronic dermatitis, the efficacy of which has been clinically determined, are shown in table no. 1. Alternative topical treatments whose efficacy has been established in *in vitro*, preclinical and / or clinical studies are shown in tables no. 2, 3 and 4. The alternative treatments for the treatment of AD are presented in tables no. 5, 6 and 7.

Table no. 1. Allopathic topical treatments currently applied in chronic dermatitis, the effectiveness of which has been determined clinically

Active substance/ Drug	The main action monitored and demonstrated	Mechanism of action of the drug / active substance
Pimecrolimus Tacrolimus simultaneously with topical steroids (2,15)	Treatment of AD *, psoriasis	Calcineurin ↓
Tofacitinib 2% (16)	AD treatment, Psoriasis	- JAK ↓ *: IL-21, IL-15, IL-13, IL-9, IL-7, IL-4, IL-2 * - keratinocyte regrowth, - proinflammatory factors ↓, - antimicrobial activity.
Crisaborol, 0.5% and 2% (15,17, 18)	AD treatment	- PDE4 ↓, - Adjusting the level of cAMP, - Regulation of T cell activity and TH2 * ↓, TH17 / TH22 ↓, TH1 ↓, IL-1, IL-13, IL-22, IFN-γ *, TNF * ↓.
Vitreoscilla filiformis nepatogen 5% (19)	AD treatment	- Probiotic action ↑, - Colonization of staphylococcus aureus of the skin ↓.
Ruxolitinib (20)	AD treatment	- PDE4 ↓, - JAK 1 and JAK 2 ↓.
Halobetasol (21) (Corticosteroid)	AD treatment, Psoriasis	-Antiinflammatory ↑: PLA2 * ↓, - Immunosuppressant ↑, - Anti-mitogen ↑.
PAC-14028 * 0.1%, 0.3%; 1.0% (22)	AD treatment	-Antiinflammatory ↑: TRPV1 * ↓ (PLA2 ↓, LOX 12 * ↓).
LPSp cream * (23)	AD treatment	- Interaction with cells in the stratum corneum of the epidermis, - Filaggrin ↑, - β-defensin ↑ (antimicrobial action), - TH2 ↓.

*AD - atopic dermatitis; HL: Hodgkin's lymphoma; B-cell or B-cell NHL: B-cell/T-cell non-Hodgkin's lymphoma; JAK - Janus kinase; IL - interleukin; PDE4 - Phosphodiesterase E4; cAMP – ciclic adenozine monofosfat; TH - helper T cells; TNF - tumor necrosis factor; IFN - interferon; PLA2 - Phospholipase A2; PAC-14028 - TRPV1 Antagonist (Transient Receptor Potential Vaniloid Subfamily, Member 1 (TRPV1)); LOX 12 - Lipoxygenase 12; TRPV - transient receptor potential cation channels vanilloid; LPSp - lipopolysaccharide derived from Pseudomonas Agglomerans.

Table no. 2. Alternative topical treatments currently applied in chronic dermatitis, the efficacy of which has been determined in vitro

Active substance	The main action monitored and demonstrated	Mechanism of action of the drug / active substance
Fenolia® Eudermal Cream 15 (HT * formulation) (8)	- RHE thickness *, - Adequate maturation and protein expression, - Antiinflammatory action, - HT availability.	- RHE thickness: Cell proliferation (Ki67 *) ↑, - Adequate maturation and protein expression (Loricrin, Fillagrin, E-Cadherin and Cytokeratine 5 and 6 ↑), - Antiinflammatory (IL 1 * ↓, IL 8 ↓), - Transcutaneous absorption for HT ↑.

* HT - hydroxytyrosol; RHE - reconstituted human epidermis; IL-interleukin; Ki67 - nuclear protein that encodes the MKI67 gene.

Table no. 3. Alternative topical treatments currently applied in chronic dermatitis, the efficacy of which has been preclinically determined

The product/ preparation, dose, method of administration	Preclinical determinations of efficacy of products / preparations						
	Pathology followed	Species / Line, sex, age (Seven weeks)	No. of Animals / No. of Groups	Period (number of days)	The mechanism of pathology induction	The main action monitored and demonstrated	Product / Mechanism of Action preparation
Eupatiline 1% * (10)	AD*	Lab rats NC / Nga male, 4	5 animals / group; 4 groups	29	DNCB*	Clinical severity score for AD	- T-SLP *, TNF-α *, Th2 *, IL-4 *, IL-19 ↓, - Hyperkeratosis ↓.

*AD - atopic dermatitis; Eupatiline – 2 - [3,4-dimethoxyphenyl]-5,7-dihydroxy-6-methoxychromen-4-one (a lipophilic flavonoid obtained from medicinal plants of Artemisia umbelliformis Lam. and Artemisia genipi Weber); DNCB-1-chloro-2,4-dinitrobenzene; T-SLP – thymic stromal lymphopoietin; TNF - tumor necrosis factor; Th - helper T cells; IL - interleukin.

Table no. 4. Alternative treatments for the treatment of chronic dermatitis, the efficacy of which has been determined preclinically

The product/ preparation, dose, method of administration	Preclinical determinations of efficacy of products / preparations						
	Pathology followed	Species / Line, sex, age (Weeks)	No. of Animals / Nr. of Groups	Period, no. of days	The mechanism of pathology induction	The main action monitored and demonstrated	Mechanism of action a product / preparation
PTQX (1), 8.0 g / kg c, dissolved in water, 20 ml / kg	AD*	Lab rats NC / Nga, male, 6-8 weeks	7-8 animals / group; 4 groups	21	- DNCB determines ↓ release of endogenous and exogenous histamine *, - Inflammatory effects: > edema with xylene	- Inflammation of CD4 + * and CD8 T cells in skin lesions ↓, - IgE production * in serum ↓,	Mast cell infiltration into skin lesions ↓

					inserted into the ear, > inflammation with acetic acid in the permeable capillaries of the abdomen.	- Swelling of the ear ↓, - Adjusting the balance of Th / Treg cells *	
		Lab rats C57BL / 6	7-8 animals / group; 4 groups	21	Differentiation of Th1 and Th2 cells	Balance adjustment between Th1 and Th2	
Balance adjustment between Th1 and Th2	AD, Psoriasis	BALB / c females 7 weeks us	8 animals / group 4 groups	31	DNCB application	- MDC * ↓ - phosphorylated STAT1 * (tyrosine 701 and serine 727), - Phosphorylation ERK 1/2 * ↓, - IgE * ↓.	Action on skin keratinocytes
Vinegar (11)	AD	Lab rats Murinae, females, NS *	6 animals / group 5 groups	21	Topical application 0.1% Ox *	- Edema, scales, lichenification ↓, - Epidermal permeability ↑, - Skin hydration ↑	Changing the pH of the skin

*AD - atopic dermatitis; PTQX – TCM Pei Tu Qing (phytotherapeutic preparation from traditional Chinese medicine recommended in the treatment of AD); DNCB-1-chloro-2,4-dinitrobenzene; IgE - Immunoglobulins, CD - cluster of differentiation; Th - helper T cells; Treg - regulatory T cells; MDC - inflammatory chemokines; STAT 1 - Signal translator and transcription activator 1; ERK 1/2 - Kinases regulated by extracellular signal (synonym for mitogenated protein kinase (MAPK)); Ig E - immunoglobulins E; NS - Not specified; Ox - Oxazolone.

Table no. 5. Alternative topical treatments currently applied in chronic dermatitis, the effectiveness of which has been determined clinically

Active substance	The main action monitored and demonstrated	Mechanism of action of the drug / active substance	Side effects
Enzymatically intersteratted fats (14)	AD treatment *	- Absorption into the skin ↑, - Oily deposits on the skin ↓, - Skin hydration ↑.	They were not reported
Tetramethoxyluteoline - GentleDerm® (9)	AD treatment, psoriasis, mastocytosis	- MC * ↓, - Antioxidant ↑, - Itching, - Keratinocytes ↑, - Histamine ↓, - IL-6, IL-8 *, TNFα * ↓, -Tryptase from MCs * ↓.	They were not reported

* AD - atopic dermatitis; MC - cutaneous mastocytosis; IL - interleukins; TNFα - tumor necrosis factor; MCs - neoplastic mast cells.

Table no. 6. Alternative treatments currently applied in chronic dermatitis, the efficacy of which has been determined in vitro

Active substance	The main action monitored and demonstrated	Mechanism of action of the drug / active substance
Organic oat plant extract variety Rhealba (6)	AD treatment *	-PGI2 (PG6K) * ↓; -Th1 and Th2 * ↓; - IL-2, IL-4, IL-13 * ↓;
Organic oat plant extract variety Rhealba - topic (6)	AD treatment	-TSLP * ↓; -Keratinocyte ↑; -PLA2 and COX-2 * ↓;

*AD – atopic dermatitis; PGI2 (PG6K) - prostaglandins I2, 6K; TH - Helper T lymphocytes (Th cells); IL - interleukin; PLA2 - Phospholipase A2; COX - Cyclooxygenase-2; TSLP - Thymic stromal lymphopoietin.

Table no. 7. Alternative treatments currently applied in chronic dermatitis, the effectiveness of which has been determined clinically

Active substance	The main action monitored and demonstrated	Mechanism of action of the drug / active substance	Side effects
Organic oat plant extract variety Rhealba (6)	AD treatment	- Repair of the epidermal barrier: > Keratinocyte differentiation; > Filaggrin ↑; > Epidermal lipids (ceramides, cholesterol and fatty acids) ↑; > Anti-inflammatory activity ↑ (PLA2 * ↓, COX-2 * ↓); > Immunomodulatory activity ↑ (PGI-2 * ↓, IL-2 *), MHC-II * ↓, TH2 *, IL-13 and IL-4 ↓	They were not reported

*AD - atopic dermatitis; PLA2 - Phospholipase A2; COX - Cyclooxygenase-2; PGI-2 - Prostaglandin I2; IL - interleukin; MHC-II - class of major complex histocompatibility molecules; TH - Helper T lymphocytes (Th cells).

For patients suffering from AD and wanting alternative treatments instead of allopathic ones, there are products based on PTQX (1), organic oat plant extract variety Rhealba (6), organic oat plant extract variety Rhealba - topic (6), camphor tree (Cinnamomum camphora) - leaves, 80% alcoholic extract (7), Fenolia® Eudermal Cream 15 (hydroxytyrosol-based formulas) [8], enzymatically interspersed fats (14), tetramethoxyluteoline - GentleDerm® (9), Eupatiline 1% * (10), vinegar.(11) In the case of products with natural extracts, flavonoids have an anti-inflammatory role with positive effects in the treatment of DA. The strong anti-inflammatory (PLA2↓, COX-2↓) effect of the organic oat plant extract variety Rhealba (6) is determined by flavonoids (polyphenols) and saponins (polar molecules). And in the case of GentleDerm® (9), flavonoids have anti-inflammatory action, tetramethoxyluteoline being a natural flavonoid with antioxidant properties. Another flavonoid that enhances DA is eupatilin (5,7-dihydroxy-30,40,6-trimethoxyflavone).(10)

In clinical practice, the treatment of AD in some cases can be quite difficult, both due to frequent recurrences and the use of various cosmetics with perfumes (detergents, balms, soaps etc.).

CONCLUSIONS

An important role belongs to the dermatologist in the control of the acute phase of AD but also later in the maintenance of atopic skin with special care products with calming, emollient and moisturizing effects, which do not destroy the hydro-lipid barrier and thus affected in AD.

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