New combined topical therapy for refractory rosacea

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Abstract The main pathogenetic aspects of rosacea, various classifications of the dermatose and the modern clinical classification are presented. The symptoms of different forms of rosacea are described. Contradictions of modern scientific concepts of different researchers, approaches to etiology, pathogenesis and treatment are discussed. The social significance of rosacea, the importance and possibility of eliminating the symptoms of the disease at early stages, the achievement and prolongation of remission are shown. The main triggers of manifestations of rosacea, which should be taken into account to achieve the maximum effect of the treatment of a disease are indicated. The first national positive experience of authors with combination of ivermectin 1% cream and tacrolimus 0,03% ointment is presented. The high clinical efficiency and very good tolerability of this combination, compared to monotherapy of ivermectin 1% cream and conventional therapy of metronidazole cream and azelaic acid gel as well as the absence of any side effects in patients with moderate to severe rosacea are shown.

Index Terms: Rosacea; Acne Rosacea, Guttarosacea, Cuperose, Teleangiectasiasis Faciei; Topical Treatment; Ivermectin; Tacrolimus.

1. INTRODUCTION

Rosacea (pink acne, red acne, acne rosacea, guttarosacea, cuperose, teleangiectasiasis faciei) is a well-known, chronic, inflammatory dermatose of multifactorial origin, characterized by facial erythema and papular-pustular eruptions.

Rosacea is more typical for fair skinned people (I, II, rarely III phenotype in Fitzpatrick classification) [1], mainly women of 30-50 years old whereas its more severe form – rhynophyma – is frequently seen at men [2].

According to epidemiological data from the USA and Europe rosacea is diagnosed in 3-22% of population. In 2015 the data of RISE (Rosacea International Study on Epidemiology) indicated the rosacea population rate of 12,3% for Germany and 5,0% for Russia. This report also indicated high sensitivity level of 83% of rosacea patients skin to external (environmental) factors [3].

Rosacea exclusively affects the face that is immediately seen by surrounding people that leads to social discomfort of the patients. Most of them tend to suffer a lot and "get down to their disease", cut social activity, get depressed and in severe cases may manifest nosogenic reactions as psycho damaging factor.

Rosacea is friquently very difficult to treat disease which makes patients distrust doctors and this consequently creates the so called "vicious circle" and the situation gets worse.

Rosacea is a complicated, unpredictable, sometimes refractory to treatment disease. Its development depends on genetic predisposition and phenotypical triggers. Genetic factors influence vascular features (angioneurosis) and immune characteristics. One of the main negative factor is a high level of antimicrobial peptides – katelizidines which catalysis inflammatory reaction with neutrophils, T-sells and dendritic cells [4]. Phenotypic pattern is determined by genetic which means symptoms of dermatose is a reaction on usual environmental influences such as high temperature, ultraviolet, etc. which is typical for patients predisposed to rosacea [3].

Unfortunately not all pathogenic mechanisms are well understood but most researches agree on the fact that the disease is provoked by high facial vascular sensitivity [5,6]. It was shown that blood flow is much stronger in rosacea patients than healthy people. Besides, the skin superficial vascular net is permanently increased with the vessels diameter getting larger than normal ones [7].

There are some reports on vascular endothelial growth factor – VEGF and its influence on rosacea development. It is produced by keratinocytes and could be upregulated by both endogenic and exogenic triggers. In rosacea skin its level increases from 55,6 to 88,9 % [8]. VEGF leads to vascular dilation, permeability increase and frequent flashes. There is also strong direct link between disease duration and VEGF level [9].

The other flash provoking factors could be divided into two main groups: endogenic and exogenic. Endogenic factors are endocrine, psychosomatic, immune (lymphocytes, antibodies, collagen of IV type, circulated immune complexes, proven increase in CD3 and CD4 T-lymphocytes along with decrease in CD8 T lymphocytes which indicates autoimmune activity), gastrointestinal diseases with H. pilori infection, Demodex folliculorum mite, kallecrein-kinin system activation and bradikinin increase.

Exogenic factors mean physical influence (insolation, strong wind, high temperature, radiation), active physical exercises, irritating cosmetic products, uncontroled use of topical glucocorticosteroid drugs, hot meals and alcohol, etc [10,11].

There are different rosacea classifications based on different criteria. The ISCD-10 (rosacea, rhinophyma, another kind of rosacea, rosacea of unidentified kind) is an example of a statistical classification internationally accepted.

There is a classification based on disease stages:

prodromal stage, hot flashes;

stage I: clear erythema, telangiectasia;

stage II: clear erythema, telangiectasia, papules, small

pustules;

stage III: clear bright erythema, intensive telangiectasia, papules, pustules, ganglions; sometimes infiltrates in central part of the face [11].

Nowadays, the classification based on clinical subtypes of the disease looks practically more reasonable and comprises 4 variants: erythematotelangioectatic, papular-pustular, phymatose and ophthalmorosacea.

According to National rosacea society [12] the classical stages of the disease development do not exist and the same patient could demonstrate several stages at a time.

Rosacea is diagnosed clinically according to some primary and secondary symptoms (not less than two primary and two secondary) [12].

The primary symptoms are:
flushes (erythema);
constant erythema;
papulars and pustulars;
telangiectasia.
The secondary symptoms are:
burning and tingling;
papulars and pustulars making plaques;
dryness;
swelling;
eyes irritation;
phymatose changes .

Rosacea treatment is well presented in multiple guidances, monographs, articles. On the one hand, there is so called "rosacea treatment standard" comprising a limited number of medicines for rosacea patient treatment, and on the other hand, there are medical recommendations (national, international) which describe wide variety of therapeutic technologies clinical dermatologist could use for a particular patient.

Russian national medical recommendations [13] presumes the following:

Systemic drugs:
antibiotics (doxycycline, erythromycin, clarithromycin);
group 5-nitroimidazole (metronidazole, ornidazole);
retinoids (ithotretinoin);
angiostabilising medicines (belladonna alkaloid + phenobarbital, ergotamine and xantinol nicotinate).

Topical preparations:
metronidazole;
azelaic acid;
antibiotic (clindamycin);
benzoyl peroxide;
topical retinoids;
topical calcineurine inhibitors (pimecrolimus and tacrolimus).

International guidelines recommend [14,15]:

Systemic drugs:
antibiotics (tetracycline);
antimicrobial drugs (metronidazole);
retinoids (isotretinoin).

Topical drugs:
azelaic acid;
metronidazole;
10% sulfacetamide sodium with 5 % sulfur;
ivermectin;
brimonidine tartrate.

Though dermatologists can prescribe different medicines to treat rosacea patients, a great number of cases of long lasting rosacea with strong resistance to any treatment could be observed.

After trying the whole spectrum of a well known "drug list" and constant failures such patients tend to get more depressed and give up treatment. For these clinically severe cases it is highly necessary to find out new approaches and treatment methods.

The FDA approval of ivermectin 1% cream for rosacea is a good confirmation of this necessity. The drug was registered in Russia in 2016 and has successfully demonstrated its high clinical effectiveness [16].

The ivermectin 1% cream is quite a new medicine for rosacea with dual activity: antiparasitarial and antiinflammatorial. It belongs to a group of polysynthetic endectocides of macro cycle lactones produced by bacteria Streptomyces avermitili. Earlier it was used as a treatment of endoparasitic and topicaly for exoparasitic invasions in animals. The mechanism of action of ivermectin consists in blockage of specific channels for signal transmission in neural synapse of Invertebratas, which leads to their paralysis and death (for example, worms, acarian, lice which are parasites in mammals including humans).

Topical ivermectin is known with its antiacarian effect against Demodex folliculorum in cases of so called "demodecosis". A higher number of this mite in the facial skin is more typical for rosacea patients than for other people. So as antiinflammatory activity of the ivermectin was already known, it could be explained by abovementioned effects. And it should be added that Demodex folliculorum is not necessarily present in all cases of rosacea [16].

Antiinflammatory activity of ivermectin is based on suppression of T-cells and immune humoral response, decrease of neutrophil phagocytes, chemotaxis and oxidants production by phagocytes; on regulation of TNFα production, IL -1β and IL -10 in lipopolysaccharide dependent inflammation, proven in vitro research [3].

In 2011-2013 in the USA and Canada double blind RCT were carried out [17], which demonstrated high effectiveness of ivermectin 1% cream comparing to placebo cream when it was applied once a day/night to treat moderate to severe papular-pustular rosacea (n=1371). In all trials the rate of successfully treated patients (clear and almost clear results of IGA), was much higher in groups of ivermectin 1% cream than in placebo groups: 38,4 and 40,1%; 11,6 and 18,8%. Moreover, the clinical efficiency of ivermectin was characterized by rare topical unwanted reactions (burning, itching), and the absence of severe side effects.

Aiming at successful topical treatment of refractory rosacea we proposed and patented (Pat. № 2645932 dd 28.02.2018) a new combination of two topical drugs - the ivermectin 1% cream and tacrolimus 0,03% ointment for severe cases of erytematopapular rosacea which in our opinion could give good clinical results and prolong remissions.

Tacrolimus is a well known non-steroidal antinflammatorial preparation of natural macrolides group with immunosuppressive activity. Tacrolimus suppresses the activity of T-lymphocytes, decreases production of interleukins, TNFα, IgE receptor sensitivity of antigen cells, prevent degranulation of mast cells and basophiles [18].

The tacrolimus ointment is registered in Russia for the atopic dermatitis treatment. Hence, according to Russian national recommendations it could be used in rosacea patients as well.

Main advantages of combination the ivermectin 1% cream and the tacrolimus 0,03% ointment are:

high antiinflammatory effect;

prolong remission, control and prevention of disease attack;

once daily application (for each drug) comfortable for patients.

The purpose of this pilot research was to evaluate effectiveness and safety of combined application of the ivermectin 1% cream and the tacrolimus 0,03% ointment comparing to classical approach to treat patients with erythematous-papular rosacea of moderate severity.

2 Materials and methods. Subjects, treatments and assessments

We monitored 75 patients of 30-50 years old with confirmed diagnosis of "erythemato-papular rosacea of moderate severity" refractory to previous treatment. The disease duration was 2-11 years (5,5±1,25). Before inclusion into the trial all patients were treated topically (metronidazole, adapalen, benzoyl peroxide, fusidic acid, etc) and/or used if necessary systemic drugs (retinoids, antibiotic of tetracycline group, metronidazole). The treatment outcome was not satisfactory.

If indicated some patients were treated with gastrointestinal drugs, antihistamines and sedatives.

The Investigator's Global Assessment (IGA) was performed at week 0 and week 8 to evaluate the clinical efficiency of the treatment. The disease severity was defined by erythema grade and the number of papules/pustules on each of five facial zones: forehead, chin, nose, right cheek, left cheek. Moderate stage was characterized by modest erythema without clear edges covering 1/3-1/2 of cheek with few telangiectasia and papules; for more severe stage the pronounced erythema covering the whole cheeks with multiple telangiectasia and papules were the main criteria.

The dermatology life quality index was also used to measure the skin symptoms of rosacea influence on patient's quality of life before and at the end of the trial. Safety control comprised monitoring of all side-effects and symptoms of topical intolerance of medication (burning, drying, itching).

The research was randomized and in 3 parallel groups. In group 1 (25 patients) the patients were treated with ivermectin 1% cream (in the morning) and tacrolimus 0,03% ointment (at night).

In group 2 (25 people) the patients applied ivermectin 1% cream in the morning and regular cosmetic cream as emollient instead of tacrolimus in the evening.

In the control group 3 (25 people) patients were treated with metronidazole 1% cream (in the morning) and azelaic acid 20% gel (in the evening).

All topicals were applied with thin layer on each of 5 face zones (forehead, cheeks, nose, chin), excluding eyes and lips.

During the whole period of the trial all patients were advised to avoid any trigger factors potential to aggravate the disease: diet, sunscreens, cold wind, intensive physical exercises etc.

All observed patients had almost identical rosacea symptoms before the treatment: most patients were diagnosed with moderate stage rosacea (28±11,7 inflammatory lesions with mild erythema). DLQI before the treatment was 18±1,0, which means considerable influence on patient's quality of life.

3 Results

3.1 Efficacy

The percentage of patients who reached "clear" or "almost clear" level at the end of 8 week period in group 1 was 92%, in group 2 - 68%, and in group 3 - 52%.

The marked difference between groups were already observed at the 4th week of treatment (76%; 60% and 44% respectively) (Figure 1).

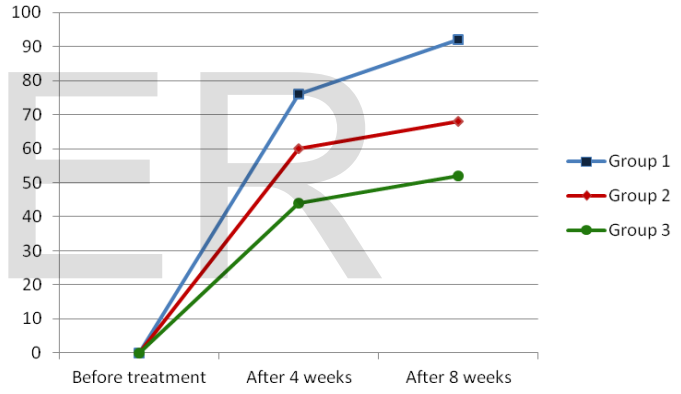


Fig. 1. The percentage of patients who reached "clear" or "almost clear" at week 8

The number of inflammatory lesions at week 8 decreased on 25,5±1,5 for group 1, on 20,3±1,2 for group 2 and on 15,2±0,9 for group 3; showing the reduction of inflammation in 91,07%, 72,5% and 54,28% respectively ($p < 0,05$) (Figure 2).

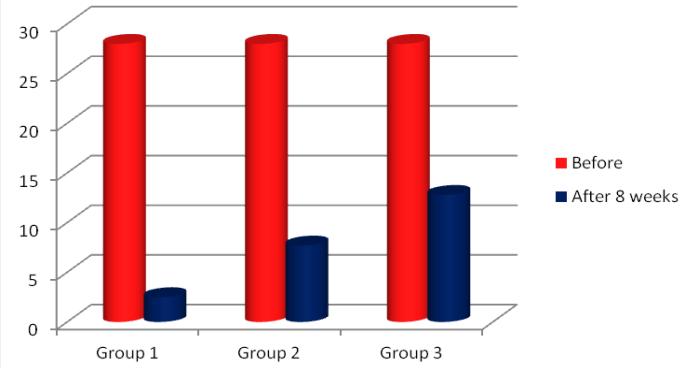


Fig. 2. Number of the inflammatory lesions decreased at week 8

At the week 8 DLQI in group 1 was 3 points, in group 2 - 4 points and in group 3 - 8 points which means minimal influence on patient's quality of life in groups 1 and 2 and moderate influence for group 3.

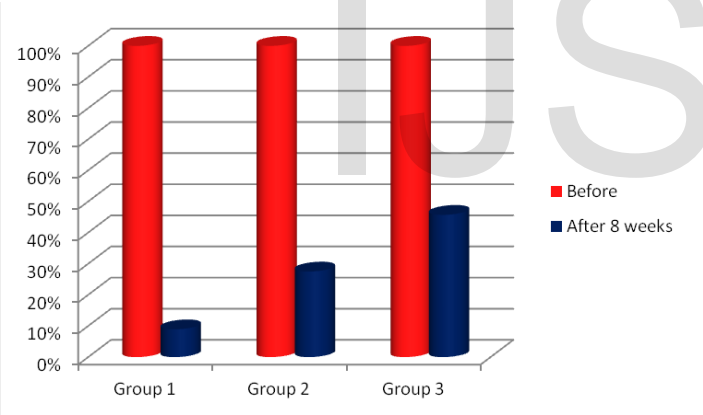
3.2 Safety

All treated patients showed very good drug tolerance and experienced no side-effects. Two patients complained on oily shine of the face after tacrolimus ointment application and were advised to apply thinner layers.

After the main treatment cessation the patients of group 1 were advised to apply tacrolimus 0,03% ointment as maintenance therapy gradually decreasing applications: from every other day during the first month to twice or once a week during next month till permanent cessation in case of rosacea symptom absence.

4 Discussion

Summarizing the results of the trial we conclude that combined therapy of patients with refractory erythemato-papular rosacea with ivermectin 1% cream and tacrolimus 0,03% ointment is much more efficient in terms of time and clinical effect comparing to monotherapy with ivermectin 1% cream. Conventional combined therapy of rosacea with metronidazole 1% cream and azelaic acid 20% gel is less effective comparing to those with ivermectin. "Clear" or



"almost clear" results at week 8 of the trial were observed in 92% of patients from group 1 (Figure 3, 4, 5, 6, 7), in 68% - from group 2 and in 52% of patients from group 3. The first visible differences between the groups were already observed at week 4 of the treatment.

Fig. 3. Percentage of reduction of the inflammatory lesions at week 8

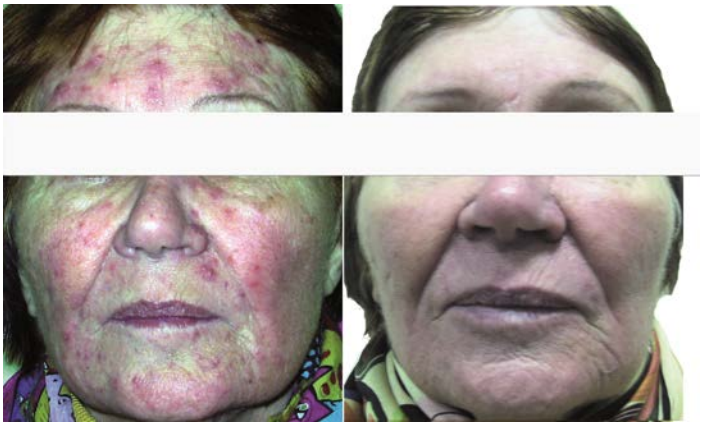


Fig. 4. Patient B. Erythemato-papular rosacea (few pustules). Combined therapy with ivermectin 1% and tacrolimus 0,03% (before treatment and after 8 weeks)

Fig. 5. Patient C. Erythemato-papular rosacea. Combined therapy with ivermectin 1% and tacrolimus 0,03% (before treatment and after 8 weeks)

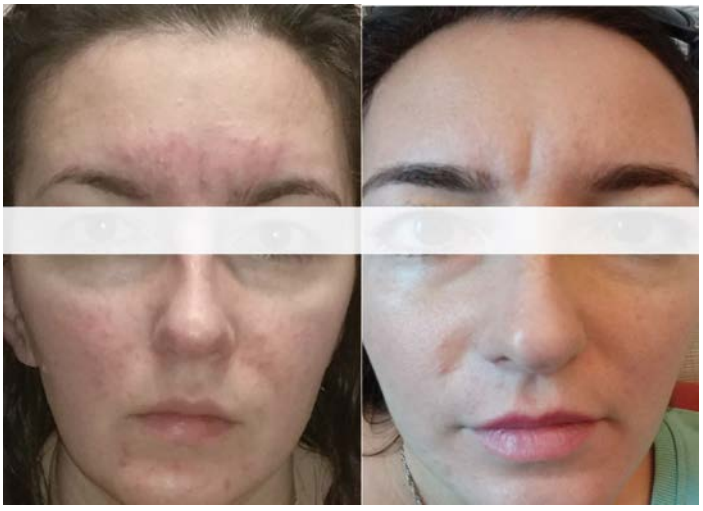


Fig. 6. Patient A. Erythemato-papular rosacea . Combined therapy with ivermectin 1% and tacrolimus 0,03% (before treatment and after 8 weeks).

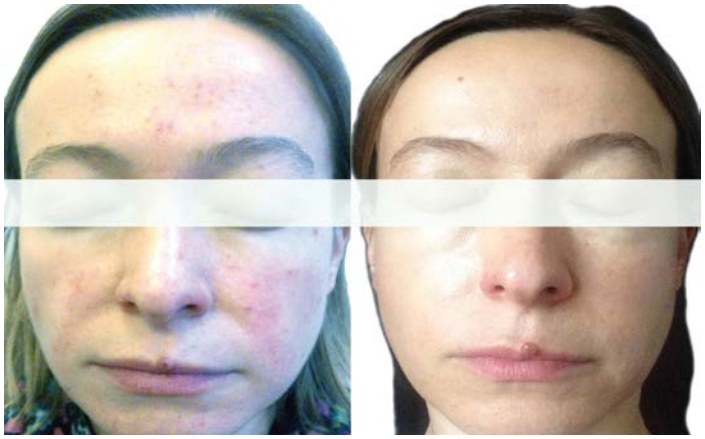


Fig. 7. Patient T. Erythemato-papular rosacea. Combined therapy with ivermectin 1% and tacrolimus 0,03% (before treatment and after 8 weeks)

According to our results we could recommend the combination of ivermectin 1% cream and tacrolimus 0,03% ointment as one of the most effective topical treatment of patients with erythemato – popular rosacea refractory to conventional medication.

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