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Rosacea – clinical manifestation and therapeutic options

Trądzik różowaty – objawy kliniczne, możliwości terapeutyczne

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Summary

Rosacea is a chronic inflammatory skin disease affecting the central part of face and characterized by erythema, teleangiectasia, papules, pustules and edema. Although the disorder is common in adult population its etiopathogenesis as well as pathophysiology is not entirely elucidated yet.

Possible pathogenic roles have been suggested especially for vascular abnormalities, neurogenic inflammation and altered innate immune response to heterogenous stimuli. Genetic and environmental factors are believed to influence the onset and clinical development of rosacea, among them immunological, bacterial/infectious, endocrine, pharmacological, climatic, thermal and dietary triggers. The prevalence of rosacea is highest among Caucasians of Celtic and northern European origin, occurring more frequently in women of 30-50 years of age. Clinical manifestation of disease includes four main subtypes: erythematoteleangiectatic, papulopustular, phymatous and ocular. Additionally rare variants can be observed, among them: granulomatous rosacea, rosacea fulminans, Morbihan disease and steroid rosacea. Ocular involvement with dryness, blepharitis, conjunctivitis, iritis and keratitis is found in about half of the patients. Various therapeutic strategies are possible, including avoiding the triggering factors, topical and oral options and the use of laser surgery. The choice of therapy depends on the severity of the clinical symptoms, subtype of rosacea and needs to take into consideration the psychological impact of the disease. Topical therapy (metronidazole, azelaic acid, erythromycin, clindamycin, benzoyl peroxide, tacrolimus, retinoids) is often sufficient, but in severe rosacea can be combined with systemic treatment (tetracyclines, metronidazole, macrolides, isotretinoin, laser therapy).

Streszczenie

Trądzik różowaty jest przewlekłą zapalną chorobą skóry zajmującą środkową część twarzy i charakteryzującą się występowaniem rumienia, teleangiektazji, grudek, krost i obrzęku. Chociaż choroba jest częsta u osób dorosłych, jej etiopatogeneza, jak również patofizjologia nie są całkowicie wyjaśnione. Przypuszcza się, że rolę patogenną mogą szczególnie odgrywać zaburzenia naczyniowe, neurogenne zapalenie i zmieniona wrodzona odpowiedź immunologiczna na różnorodne bodźce. Uważa się, że na wystąpienie i rozwój kliniczny trądziku różowatego mogą wpływać czynniki genetyczne i środowiskowe, wśród nich czynniki immunologiczne, bakteryjne/infekcyjne, endokrynne, lekowe, klimatyczne, termiczne i dietetyczne. Największa częstość występowania trądziku różowatego obserwowana jest wśród osób rasy kaukaskiej pochodzenia celtyckiego i północnoeuropejskiego, a zwłaszcza u kobiet w wieku 30-50 lat. Wyróżnia się cztery główne odmiany choroby: rumieniowo-teleangiektatyczną, grudkowo-krostową, przerosłą i oczną. Ponadto, występować mogą także rzadkie warianty, takie jak postać ziarniniakowa, posterydowa, *rosacea fulminans*, choroba Morbihana.

U około połowy pacjentów stwierdzane są objawy oczne, w postaci suchości, zapalenia brzegów powiek, zapalenia spojówek, zapalenia tęczówki i rogówki. Dostępne są różne opcje terapeutyczne, zaczynając od unikania czynników prowokujących, przez miejscowe i ogólne metody leczenia do zastosowania zabiegów laserowych. Wybór metody leczenia zależy od ciężkości objawów klinicznych, odmiany trądziku różowatego oraz musi także uwzględniać psychologiczny wpływ choroby. Leczenie miejscowe (metronidazol, kwas azelainowy, erytromycyna, klindamycyna, nadtlenek benzoilu, takrolimus, retinoidy) jest często wystarczające, lecz w trądziku o ciężkim nasileniu powinno być skojarzone z leczeniem ogólnym (tetracykliny, metronidazol, makrolidy, izotretynoina, laseroterapia).

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Rosacea is a chronic inflammatory skin disease affecting the central part of face and characterized by erythema, teleangiectasia, papules, pustules and edema. The condition usually occurs in adults, although very rarely children may also be affected (1-4).

Epidemiological data coming from the American and European studies are divergent. Some data report the incidence of rosacea as 1% of the disorders diagnosed by dermatologists, or as 4000-5000 new patients cases per year (1, 2, 5, 6). The disease occurs in both men and women, but according to some authors affects both sexes equally, or much more frequently is observed in women (1, 2). It is worth to stress, that the extremely severe forms of rosacea are seen much more frequently in the male patients (1, 4, 5). Generally, the prevalence of rosacea reported to be 1-10% seems to be the highest among Caucasians of Celtic and northern European origin, occuring more frequently in women of 30-50 years of age (1, 2, 3, 6).

PATHOGENESIS

Although the disorder is common in adult population its etiopathogenesis as well as pathophysiology is not entirely elucidated yet. Possible pathogenic roles have been suggested for vascular abnormalities, neurogenic inflammation and altered innate immune response to heterogenous stimuli (2, 3, 7, 8). Genetic and environmental factors are believed to influence the onset and clinical development of rosacea, including immunological, infectious, endocrine, pharmacological, climatic, thermal and dietary triggers (3, 4, 9).

There are numerous triggering factors known, but their exact role remain to be elucidated yet. Among them, dietary factors, such as spicy foods, cheese, nuts, alcohol and hot beverages can exacerbate symptoms of rosacea, but are not considered as the primary causes (1, 3, 4, 7, 10). Apart from these, sun exposure, hot and cold weather, heat, humidity, cosmetics, medications, physical exercises, and emotional stress are recognized as the predisposing factors (1, 3, 9-11). Estonian authors have found that positive family history can be regarded the strongest risk factor for rosacea (9).

Helicobacter pylori is believed to be connected with the development or aggravation of rosacea by the release of inflammatory vasoactive mediators (histamine, leucotrienes, prostaglandines, cytokines, nitrous oxide), but its role remains still controvertial (1, 6).

Demodex folliculorum mites are suggested as another possible trigger of the skin inflammation in rosacea (1, 2, 4). Considerably increased number of mites in the skin and what is more, specific IgG antibodies against *Demodex* have been shown in rosacea patients (5, 12, 13). Additionally, *Demodex* mites are found to be a vector for bacteria *Bacillus oleronius* and its proteins can induce the immune response leading to development of papules and pustules (1, 8). Lately, the results of Whitfeld et al. suggest that in the altered milieu of the rosacea skin the commensal *Staphylococcus epidermidis* may act as a pathogenic agent and contribute to development of pustular and ocular rosacea (14). Therefore, up till now, actual role of microorganisms in the pathophysiology of rosacea has not been clearly defined. The available data suggest that they may possibly have a rather synergistic role additional to other triggering factors (6).

Although the numerous endogenous and environmental factors seem to be implicated, the exact pathogenic pathways in which these possible triggers are engaged are not entirely recognized. Pathological mechanisms of rosacea are connected with abnormalities of innative immunity, vascular changes, reactive oxygen species released by neutrophiles, inflammatory mediators, ultraviolet radiation and microorganisms (1-3, 15). Abnormal vascular reactivity seems to be the basical phenomenon in pathogenesis and vasodilatation is associated with increased levels of inflammatory mediators, including histamine, prostaglandins and reactive oxygen species (1-3, 15). Dermal extracellular matrix degeneration caused by degradative proteases released by neutrophils can additionally damage the connective tissue around the skin vessels (3). Recent data indicate that dysfunction of the innate immune system may play a central role in the development of vascular abnormalities and skin inflammation in patients with rosacea (2, 3, 10, 16). It is found that rosacea is associated with an exacerbated response by the innate immune system to environmental stimuli by releasing the elevated levels of abnormally processed cathelicidin antimicrobial peptides (1-3, 6, 15-17). It should be stressed that 10-fold higher level of cathelicidin than normal can be found in the facial skin of rosacea patients and almost 1000 times higher levels of kallikrein-5, a protease that activates epidermal cathelicidin (2, 3, 18). It seems that due to its proinflammatory and angiogenic properties cathelicidin LL-37 dysfunction may be considered as the pivotal factor in the pathogenesis of rosacea (4, 17). It is speculated wheather Toll-like Receptor-2 (TLR-2) may be involved in the patophysiological events in rosacea, because its activation can induce production of the kallikrein 5 in keratinocytes (2, 8). A suggested ligand for TLR-2 in the rosacea skin is chitin from the *Demodex mites* (2, 19).

Neurogenic inflammatory reaction is also being discussed. Some authors believe that rosacea patients are hypersensitive to physiological stimuli causing recurrent flushing of the facial skin (2, 20). In normal dermis the blood vessels, mast cells and sensory nerves are found close together, but a significantly higher number of mast cells have been reported in the skin of rosacea patients (2). So, it is speculated that the mast cells may play a role in regulation of neuroimmunological and neurovascular communication mechanisms in initial stages of rosacea (2).

CLINICAL MANIFESTATION

Clinical manifestation of rosacea is heterogenous with polymorphic lesions and various disease severity

observed. The disease usually affects the central part of the face, the forehead, nose, chin and cheeks (1, 2, 4, 21). It is worth to stress that the extrafacial location has been very rarely reported, involving neck, scalp or the chest skin (2, 22). During the chronic course the development of lesions can be observed from early transient flushing, persistent facial redness, teleangiectasia to inflammatory papules and pustules (10, 21, 23). Intermittent or chronic facial edema may also occur resulting occasionally in thickening of skin (1, 2).

There are 3 stages of clinical severity differing morphologically (1-3, 8, 21).

Stage I is characterized by recurrent epizodes of flushing easily triggered by various endogenous or exogenous stimuli. Futher, transient erythema becomes more persistent and teleangiectasia of varying severity develop (2). The patients complain of intense subjective sensations – burning, stinging, itching or dryness of the affected skin (1, 2, 20, 23).

In stage II, the persistent erythema and teleangiectasia on the center of the face with solitary or numerous red papules and pustules can be observed (1, 2). These lesions may be accompanied by lymphedema affecting the entire face as well as the involvement of adjacent skin of scalp, neck and chest (2).

In stage III, additionally to persistent erythema, papules and pustules large inflammatory nodules and hyperplasia of the connective tissue and the sebaceous glands develop (1, 2). That can manifest as diffuse skin thickening and development of inflammatory nodules, especially prominent in phymatous clinical variant of rosacea (1, 2). Involvement of the eyes as well as the psychological complications are common (1, 3, 24).

Taking into consideration the broad diversity in clinical presentation, differences in severity and type of dominating cutaneous lesions, four clinical subtypes of rosacea are proposed: erythematoteleangiectatic, papulopustular, phymatous and ocular with one variant, granulomatous rosacea (25, 26).

Erythematoteleangiectatic type is the frequently observed with its typical symptoms such as flushing, persistent central facial erythema and teleangiectasia developing on the cheeks and nose, becoming more prominent in stages II or III of rosacea (1, 24). Patients may complain of stinging or burning of the face (1, 8). What is more, patients often report that their facial skin is very sensitive to cosmetics and other topical substances (1, 24).

Papulopustular rosacea is characterized by the presence of many erythematous papules and pustules on the skin of the central face based upon the persistent erythema (1, 8, 24). Teleangiectasia, ocular involvement, facial edema can also be seen and men are usually much more affected (1). Ocular involvement is found in more than 50% of patients (1-3, 24).

What is interesting, it may precede the development of facial lesions in about 20% of rosacea patients and in primary ophthalmic rosacea, the skin lesions may be quite discrete (1, 2, 24). Among the ocular symptoms, blepharitis and conjuctivitis are the most frequently seen (1, 2, 5). Blepharitis of various severity manifests as the eyelid margin erythema, with teleangiectasia, scale, crusting, occasionally with secondary streptococcal infections (1). More severe ocular involvement with keratitis, scleritis iritis and hypopyon can also be observed (1, 6). Among them, keratitis is serious condition which may result in corneal ulceration, neovascularization, scarring and permanent damage of eyesight (1, 3). Ocular involvement is usually connected with intense subjective symptoms, such as dryness, burning, itching, foreign-body sensation, sensitivity to light (1, 2). However, there is no correlation between the severity of cutaneous and ocular symptoms (1, 2).

Phymatous rosacea is rare ultimate clinical subtype observed predominantly in men with its onset between 40 and 60 years (1, 24). The most frequently the nose is affected (rhinophyma), occasionally other areas of face, such as chin, forehead, ear or eyelid (1, 2). Patient presents thickened skin with prominent pores and irregular disturbed surface contours based patophysiologicaly on chronic edema and progressive hypertrophy of the sebaceous glands and connective tissue (1, 8). Disfiguring large nodular lesions may cause the nasal passage narrowing resulting in sleep disturbances or apnea (1).

OTHER CLINICAL VARIANTS

Granulomatous (lupoid) rosacea is a rare variant characterized by disseminated dense, brown red or yellow papules and nodules located on the cheeks, upper and lower lids and periorificial facial skin (1, 4, 24). What is important, upon diascopy, these lesions reveal a yelowish change in colour ("apple-jelly") similar to seen in lupus vulgaris and sarcoidosis (1). This condition has also typical lesions of rosacea, such as persistent erythema, teleangiectases and some more usual papules (2, 4).

Rosacea fulminans (pyoderma faciale) is dramatic variant of rosacea affecting young women (1, 2, 4). The pathogenesis is unclear, but it is suggested that rosacea fulminans may be connected with pregnancy, oral contraceptives, inflammatory bowel disease or some medications (1, 2, 8). Onset of lesions is always sudden, clinical presentation may resemble acne fulminans with large, elevated, firm, sometimes fluctuating nodules and numerous pustules. Lack of comedones and presence of erythema and teleangiectasia are typical features of rosacea and differentiate this condition from acne fulminans (1, 2).

Rosacea conglobata is quite uncommon clinical variant, unlike acne conglobata occuring only on the face (2, 4). Large inflammatory nodules, and indurated plaques can be found as well as persistent erythema and teleangiectasia (2, 4).

Steroid-induced rosacea develops as a result of prolonged application of topical corticosteroids, often as a result of misdiagnosis as "allegic disease",

or improper rosacea treatment with corticosteroids (2, 4). Severe infestation with Demodex mites is typical and difficult to eradication (2).

Morbihan disease is very rare variant of rosacea characterized by diffuse and indurated odema of the cheeks, forehead and nose and caused by the prominent involvement of the lymphatic vessels (2, 4).

TREATMENT

There are various terapeutic options available but their efficacy is not untirely satisfying. Taking into consideration, that the rosacea pathogenesis is not clear and etiology is multifactorial the choise of treatment method is not easy. What is more, the psychological impact of the disease is very important aspect of therapy, not only due to the disfiguring character of the disorder but also because long-term treatment is needed to achieve improvement or at least prevent worsening of the condition (16, 27). So, it is believed, that the most essential requirement that influence the result of therapy is the patient's compliance. Good relation between dermatologist and patient can help in the patients education and assisting in identifying the individual triggering factors (1). Patients should be advised to avoid the UV light exposition and dietary factors possibly leading to facial flushing, including alcohol drinking, hot beveriges and spicy foods (2, 4). Considering, that rosacea skin is often over-sensitive to topical substances, the proper skin-care regimen leading to normalizing of skin hydratation and reducing the alkaline pH are necessary to introduce, including the avoidance of irritating cleaners, not using soaps and peelings (2, 20, 28). The choice of treatment is dependent primarily on the severity of the disorder and its subtype (7, 24, 29). Numerous oral and topical therapeutic methods are avaliable for patients but it is well known, that various rosacea clinical subtypes respond to treatment differently.

TOPICAL TREATMENT

Topical therapy – is often sufficient with erythemato-teleangiectatic rosacea or papulopustular rosacea (2). In severe disease, it should be combined with systemic treatment. Not only the active ingredients, but also various vehicles (gel, emulsions) play a role in the tolerability and efficacy of treatment of the usually sensitive skin of rosacea patients (2).

Metronidazole

Metronidazole is the topical medication commonly used in the treatment of rosacea (2, 30). Despite its antimicrobial action, metronidazole has been shown to have considerable antiinflammatory properties (2, 3, 30). Being a strong antioxidant it can significantly reduce the generation and release of the reactive oxigen species from neutrophils, thus alleviate the tissue injury at sites of inflammation (3). Metronidazole have been shown to be effective for the treatment of moderate-to-severe rosacea of papulopustular subtype (3, 29). However, although it can improve papules and pustules and to the lesser degree also reduces erythema as well, but teleangiectasia remain unchanged (1, 3). There are numerous well documented data of the clinical efficacy of metronidazol reported in a Cochrane review (24). Generaly, metronidazol has been demonstrated to be equally effective against the papulopustular rosacea as topical azelaid acid (2). A meta-analysis assessing the efficacy for different metronidazole formulations has not demonstrated any significant differences between concentrations of 0.75% and 1% cream, gel and lotion vehicle or between one or twice daily application (31).

Azelaic acid

Azelaic acid available in 15% gel and 20% cream forms has been approved as a effective drug in topical treatment of rosacea (1, 3, 30). Its efficacy is attributed to its antimicrobial, antiinflammatory effects and the normalization of keratinization (2, 30). Due to the antiinflammatory properties azelaic acid can inhibit the production of the reactive oxygen species by neutrophiles and what is more the UVB-induced activation of pro-inflammatory cytokines IL-1, IL-6 and TNF-α (3). Last years the additional important property of azelaid acid has been recognized. It was found, that azelaic acid can decrease expression of kallikrein-5 and cathelicidin – the proteins engaged in the development of rosacea (3, 17). This finding suggests the additional mechanism of action accounting for the efficacy of azelaic acid in rosacea (3, 17). Azelaic acid is a well-tolerated preparation, but some mild-to moderate local skin reactions, such as facial burning, stinging and pruritus can occur (3, 30). Generally, this agent is considered effective and safe as a therapy for inflammatory papulopustular rosacea (1, 20). What is important, azelaic acid does not promote bacterial resistance (1, 3). The recommended application of azelaic acid 15% gel is twice a day in moderate inflammatory rosacea within 12 weeks (1).

Clindamycin

Topical clindamycin (1%) is used in rosacea therapy due to its antimicrobial and antiinflammatory activity (2-4). When applied alone, clindamycin has been shown to reduce the number of papules, pustules and nodules, but used in combination with other topical agents produce much better clinical results (2). Combination of topical clindamycin 1% with benzoyl peroxide 5% was appeared to be more effective than clindamycin alone (3). It has been reported that, the clindamycin lotion achieved similar clinical improvement to oral tetracycline and was superior in the eradication of pustules (32).

Topical retinoids

Topical retinoids have their limited use in the therapy of rosacea. There are some controversies connected with their possible usefulness because of the well

known irritant activity especially in patients with sensitive skin (3, 29). Therefore, it is suggested that retinoids, being effective against papular and pustular lesions can at the same time worsen the underlying vascular abnormalities, especially can increase angiogenesis and cutaneous vascularity leading to the development of teleangiectasia (1, 3, 29). Taking into consideration these possible disadvantages, tretinoin, retinaldehyde, tazarotene and adapalene were tried, but there are few documented data to support their use, so the actual evidence-based efficacy has not been assessed (1). According to the other opinions, topical retinoids appear to be beneficial in treating severe papulopustular or recalcitrant rosacea (3). Among the retinoids compounds, adapalene shoud be preferable due to its better tolerability to the sensitive skin (2, 4, 33). It has been found, that compared with metronidazole, adapalene has been more effective in reducing the inflammatory lesions, but less effective in reducing erythema and the onset of improvement may be delayed (1, 2).

Calcineurin inhibitors

Topical tacrolimus and pimecrolimus have been studied for use in rosacea because of their anti-inflammatory effects by inhibiting T-cell activation and cytokine release (1, 7, 34). The efficacy of therapy has been found different in various subtypes of the disease. According to some reports, treatment of papulopustular rosacea with tacrolimus can reduce erythema, but it has had no effect on the papulopustular lesions (2). 1% pimecrolimus cream is regarded as safe and effective therapeutic option for the treatment of mild to moderate rosacea (34). It seems, that the most promising use of the calcineurin inhibitors concerns steroid-induced rosacea (2). Some reports have found that both tacrolimus 0.03% or 0.1% ointment as well as 1% pimecrolimus cream can be effective in steroid-induced rosacea and in granulomatous rosacea (1, 2).

Benzoyl peroxide can be tried with caution in patients suffering from rosacea who do not have sensitive skin; in such patients it may lead to an improved appearance of the skin (2, 4).

Permetrin 5% cream (not avaliable in Poland) is applied in the treatment of rosacea in patients with heavy infestation with *Demodex* mites, because of its antiparasitic effect (1, 2, 4). It is believed that used as the adjunctive agent permetrin cream can alleviate the skin inflammation.

Topical vasoconstricting agents

Brimonidine 0.5% gel is a highly selective α-2-adrenergic receptor agonist that is effective against symptoms of flushing and erythema (1, 2). One daily use of drug can bring several-hour-lasting vasoconstriction, thus it can be adjunctive in erythematoteleangiectatic subtype of rosacea (2).

Good effects has been found using topical xylomethazoline due to its well known vasoconstricting properties (35). Erythematoteleangiectatic rosacea has been reported to be effectively improved by xylomethazoline (35).

Topical treatment of ocular rosacea

Ocular rosacea needs careful treatment by both dermatologist and ophtalmologist. Lid hygiene and warm compresses can alleviate subjective symptoms (1). Artificial tears are often necessary for dryness of eyes (1).

Various methods of treatment may be needed according to the severity of the ocular involvement, including topical corticosteroids combined with antibiotics, fucidic acid and metronidazole gel applied to lid margins (1, 4, 7).

SYSTEMIC TREATMENT

Systemic therapy is necessary for severe refractory forms of rosacea (2). Several oral agents have been used, among them antibiotics, retinoids, oral vasocontrictors (1, 2, 4, 7, 24). Oral antibiotics are regarded as effective therapeutic option for rosacea and are thought to act mainly through their antiinflammatory properties (1, 2, 7, 30). Not all clinical subtypes respond equally to this method of treatment. Numerous data indicate that antibiotic therapy is most effective against inflammatory papulopustular rosacea with minimal effects on erythema and lack of effect on teleangiectasia (1, 7).

Tetracyclines

Tetracyclines are used as the antibiotics of choice for the treatment of rosacea especially for the papulopustular type (1, 7). The efficacy of tetracyclines in skin diseases including rosacea is dependent on their non-antimicrobial action, such as the ability to reduce the inflammatory response (1, 2, 29). It has been found that tetracyclines can not only down-regulate the production of proinflammatory cytokines, such as IL-1 and TNF-α but also they can inhibit angiogenesis, neutrophile chemotaxis, reactive oxygen species and the matrix metalloproteinases (1-3). Last years, a lot of new evidences accumulate documenting spectrum of antiinflammatory and immunomodulating properties of the tetracycline group, especially doxycline. Results of the studies have indicated that doxycycline can interfere with the pathophysiology of rosacea by inhibiting the proteolytic activation of kallikrein-related peptidases, which results in preventing the cathelicidin activation (2, 7, 10, 36).

Tetracycline administered in a dosage of 1000-250 mg per day has been used for decades in the treatment of rosacea (2). There is an opinion, that twice daily administration of 250 mg for 4 weeks can bring significant improvement of skin lesions in majority of patients with papulopustular rosacea (2). Further improvement of the disease and remission may be achieved with daily administration or taking 250 mg tetracycline every other day (2). However, the recurrence after discontinuing of treatment occurs frequently (2).

Newer generation tetracyclines, including minocycline (not avaliable in Poland), doxycycline, limecycline,

are similarly effective in treating inflammatory rosacea (1, 2, 8). What is important, compared to first generation tetracyclines, they have better pharmacologic properties, such as improved bioavailability, longer half-life and they can be taken with meals, minimizing gastrointestinal discomfort (1, 2). Doxycycline and minocycline may be used in the treatment of rosacea at a daily dosage of 100-200 mg but it appeared that doxycycline has a better side effect profile than minocycline (2). It is worth to stress, that the anti-inflammatory dose for doxycycline is 40 mg per day, so there is a 40 mg formulation of this medicine prepared for the treatment of inflammatory skin disaeses (not avaliable in Poland yet) (1, 8, 30).

Macrolides

Macrolide antibiotics, including erythromycin, clarithromycin and azythromycin should be reserved for special conditions, such as intolerance, resistance, allergy to tetracyclines, contraindications such as pregnancy, lactation or age younger then 12 years (1-3, 8, 29). For these group of rosacea patients macrolides are possible alternatives, despite some disadvantages, such as the gastrointestinal side-effects (2, 3, 24).

Oral erythromycin is an effective drug for the treatment of papulopustular rosacea in doses of 250-1000 mg daily, but is not frequently recommended due to its discomforting side-effects (1, 2, 24). Second generation macrolides – claritromycin and azithromycin are not only better tolerated than both tetracyclines and erythromycin but also produce clinical improvement more quickly (1, 24). It has been found that clarithromycin at a dose of 250 mg every other day for four weeks, followed by once daily administration of 250 mg for four weeks can be effective in reducing erythema and papules, and these effects were more quickly observed than with doxycycline (2, 4).

Good clinical results have been reported in rosacea patients treated with azythromycin. Azythromycin (500 mg three times a week) has been shown to be at least as effective as doxycycline (100 mg daily) in reducing the papulopustular lesions of rosacea (1, 37).

Oral metronidazole is a treatment option alternative for rosacea patients who do not respond well to tetracycline (4, 7, 29). This antimicrobial medicine has proved to be effective mostly due to its antiinflammatory activity, such as inhibition of release of the reactive oxygen species from neutrophiles (1, 3). Metronidazole can reduce inflammatory lesions and perilesional erythema of papulopustular rosacea (1). Metronidazole at a dosage of 200 mg given twice daily for 12 weeks has been found to be equally effective as oxytetracycline 250 mg given twice daily (2). It worth to stress, that patients should be strongly advised to avoid alcohol drinking during treatment with oral metronidazole (1-3).

Oral isotretinoin can be a valuable treatment option for severe rosacea refractory to other methods (1-4). What is especially important, it proved to be effective in various clinical subtypes of the disease, not only in papulopustular, but also in erythematoteleangiectatic, granulomatous as well as in phymatous or in extrafiacial forms of the condition (1, 2, 38). For the most severe subtypes, such as rhinophyma, granulomatous rosacea and rosacea fulminans, oral isotretinoin is regarded as the treatment of choice (1, 7). It is well known, that in rosacea isotretinoin can bring improvement being used in much lower doses compared with used in acne. Isotretinoin has been found to be effective in reducing rosacea symptoms taken at daily doses of 0.2-0.3 mg/kg, what is more at the dosage of 0.3 mg/kg it proved to be not inferior to doxycycline (1, 2). Low-dose therapy is usually given for six months and is well tolerated due to mild side-effects (1, 2).

Systemic corticosteroids are indicated for use in rosacea only in the most severe clinical presentation – rosacea fulminans (2, 4). The short-term use of corticosteroids in this condition usually precedes applying of other method suitable for severe rosacea, especially the oral isotretinoin.

Beta-adrenergic blockers have been found to be effective in severe flushing reactions in the patients with erythematoteleangiectatic rosacea (1, 3, 4, 29, 39). Flushing is usually resistant to conventional rosacea treatment, it is of interest that the group of beta-blocker agents, including carvedilol, nadolol, naloxone, ondansetron, propranolol and clonidine can be potentially used for symptomatic suppressing flushing (1, 3, 29, 39).

Laser and surgical options

Lasers therapy is used mainly in treating patients with distinct subtypes of rosacea: erythematoteleangiectatic and rhinophyma (1, 2, 4, 7). These both clinical presentations are known to be poorly responding to various therapeutic options. Laser light can induce the remodelling of dystrophic dermal connective tissue and cause the superficial vessel destruction without adjacent tissue injury (1).

Pulsed dye laser, copper steam laser, kryptonite laser, pulsed neodymium-YAG laser and argon laser are found as very effective against teleangiectasia and to the lesser degree effective in improving erythema (1, 2, 4, 7). Good results of therapy for teleangiectasia with the intense pulsed light (IPL) have been also reported (2, 4). In phymatous rosacea for laser ablation the Er:YAG laser and CO_2 laser can produce very satisfying improvement, being used separately or in combination (1, 2, 4).

Rhinophyma may be also effectively treated with surgical methods, including complete excision, or incomplete excision options, such as cryosurgery, dermabrasion or electrosurgery (1, 2, 4, 7).

Finally, with the various available methods of therapeutic intervention in rosacea the choice of effective treatment should be personalized for individual patient taking into consideration disease severity, individual triggering factors, emotional impact and the patient's compliance.

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