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Review

Tetracyclines - An Important Therapeutic Tool for Dermatologist

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Abstract: Tetracyclines are a group of antibiotics whose first representative was discovered over 70 years ago. Since then, they have been of great interest in dermatology. In addition to their antibacterial activity, they are able to inhibit metalloproteinases and exhibit anti-inflammatory, anti-apoptotic and antioxidant effects. The side effects have been thoroughly studied over the years. The most characteristic and important in daily dermatolgical practice are: phototoxicity, hyperpigmentation, onycholysis, photoonycholysis, induced lupus erythematosus, idiopathic intracranial hypertension. In this article, we summarize the use of tetracyclines in infectious diseases and inflammatory dermatoses, and further discuss indications where the efficacy and safety of tetracyclines have been highlighted over the past few years.

Keywords: tetracyclines; doxycycline; limecycline; minocycline; pleiotrophy; non-antibiotic properties

1. Introduction

Tetracyclines are natural compounds produced by Streptomyces species that were discovered by Benjamin Duggar in 1948. Today we have a whole class of drugs derived from the substance discovered then.

The product of soil bacteria from the Streptomyces family was quickly subjected to careful analysis and subsequent modification. Tetracyclines began to be obtained cheaply and rapidly by fermentation.[1] This contributed to their widespread use in the treatment of human and animal diseases, animal growth promotion and aquaculture [2, 3].

The first, best characterised, representative of the group was chlortetracycline. [4] Compared to the penicillins already available at that time, chlortetracycline also had an effect on Gram-negative bacteria and was better tolerated by patients. Soon afterwards, other natural tetracyclines were isolated, including tetracycline, from which this family of molecules takes its name.

Modifications of naturally occurring tetracyclines and the synthesis of new compounds resulted in the development of new antibiotics in this group.

The development of chemically modified tetracyclines (CMT) was the most driven by common side effects of older generation tetracyclines, e.g. gastrointestinal disorders, developmental bone and tooth deformities and the development of resistant bacterial strains [5].

The tetracycline group includes tetracycline, doxycycline, minocycline, lymecycline and sarecycline.

Chemically, tetracyclic naphthacene-carboxamide ring system is the basic structure of all drugs in this group. The dimethylamine group at the C4 carbon is responsible for the antibacterial properties of tetracyclines. The removal of the side chain reduces antibacterial properties and enhances non-antibiotic activity, which was used in the production of second-generation tetracyclines [6].

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2. Mechanism of antibacterial action.

Tetracyclines passively diffuse through pores in the bacterial membrane [7]. The bacteriostatic potential of tetracyclines is based on ribosome inactivation. When bound to the 30S subunit, tetracyclines inhibit protein biosynthesis causing bacterial death.

The biological activity of tetracyclines is strongly dependent on metal chelation. In circulation the non-protein-bound fraction of tetracyclines mainly acts as ionophores for divalent metals. Ionophores are compounds capable of forming lipid-soluble complexes with metal cations [8, 9].

The lower half of tetracycline molecule is a key region for binding metal ions. Therefore, it influences the binding of bacterial ribosome, metalloproteinase-family enzymes, and mediates the mechanism of resistance [10, 11].

Calcium (Ca2+) is the main cation found in the plasma, while magnesium (Mg2+) – in the intercellular space [12, 13, 14].

In case of tetracycline, chelation also affects drug absorption in the gastrointestinal tract. Taking the drug with a meal rich in calcium leads to the formation of insoluble compounds and disruption in drug absorption. It is necessary to maintain an interval between tetracycline administration and a meal, i.e. at least 1 hour before or 2 hours after a meal. [15] Higher lipophilicity of the subsequent generations of tetracyclines provide better absorption and lower predispositions to the formation of chelates with metal ions.

TCs form a stable complex with calcium in any bone-forming tissue, tending to deposit in the areas of calcification in bones and teeth. This accumulation may be associated with adverse effects such as permanent tooth pigmentation, especially in young individuals. [16]

The extensive use of tetracyclines over the past four decades has led to the development of bacterial resistance.

The most common mechanism of the resistance of Gram-negative bacteria is associated with the membrane protein TetA, which exports the drug from bacterial cells before it manages to attack its target, i.e. ribosome [17].

The phenomenon of chelation is also of key significance in the mechanism of resistance. After binding tetracycline to a metal inside bacteria, the membrane protein starts to act as an antiporter removing the tetracycline-metal complex in exchange for the inflow of a proton [18].

Due to increasing bacterial resistance, tetracyclines lost their significance as antimicrobial drugs, but they are still extensively used due to their numerous non-antibiotic properties.

As regards clinicians, the largest quantities of antibiotics are prescribed by dermatologists with tetracyclines constituting about 75% [19].

Due to increasing bacterial resistance, tetracyclines lost their significance as antimicrobial drugs, but they are still extensively used due to their numerous non-antibiotic properties.

The interest in tetracyclines is currently directed at their non-antibiotic properties.

3. Non-antibiotic properties of tetracyclines.

3.1. Inhibiting Metalloproteinases

Matrix metalloproteinases (MMP) is a family of zinc-dependent proteases produced by inflammatory cells and connective tissue cells which participate in numerous physiological and pathophysiological processes [20].

An increased activity of metalloproteinases is observed in almost all human diseases associated with an inflammation [21].

Tetracyclines inhibit the activity of metalloproteinases binding an ion of zinc or calcium included in enzyme structure [22].

Three main classes are distinguished: collagenases, gelatinases and stromelysins. The majority of data regarding the influence of tetracyclines on metalloproteinases are

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derived from research on their use in periodontal diseases. Polymorphonuclear leukocytes (PMNs) are the main source of collagenases. They mediate connective tissue breakdown during inflammatory periodontal disease, while fibroblasts provide the collagenase necessary for connective tissue remodeling in the normal gingiva. It was demonstrated that tetracyclines did not impair the production of the enzyme by fibroblasts to ensure appropriate collagen turnover. They only influenced collagenases produced by neutrophils [23].

In addition to metalloproteinases, they also inhibit enzymes from the hydrolase group - alpha-amylases and phospholipases. Phospholipase A2 is a key enzyme in the biosynthesis of inflammatory mediators such as prostaglandins [24].

3.2. Anti-Inflammatory Activity

The broadly understood anti-inflammatory effect of tetracyclines was first observed in rosacea. The pathogenesis of rosacea has long excluded the direct involvement of bacterial factors, and yet the effectiveness of tetracyclines was observed. Today, there is ample evidence that tetracyclines reduce inflammation of various etiologies [25].

Their doses below the minimal inhibitory concentration indirectly affect inflammation by inhibiting bacterial breakdown products, which stimulate inflammatory processes.

They reduce the production of pro-inflammatory cytokines by neutrophils, such as interleukin-1β (IL-1β), IL-8, and tumor necrosis factor-α. [26]

They inhibit leukocyte migration, which occurs during the early stages of inflammation. Cell movement is inhibited by binding intracellular calcium, which is necessary for the formation of microtubules that enable cell movement. [27]

Tetracyclines reduce nitric oxide (NO) by inhibiting inducible nitric oxide synthase (iNOS) activity. The final product of iNOS is a highly cytotoxic peroxynitrite radical responsible for inhibiting collagen synthesis, proteoglycans and increasing MMP expression. Tetracyclines prevent protein denaturation by reducing peroxynitrite radicals [28].

NO likely mediates increases vessel perme-ability and edema and may support erythema development concomitant with rosacea.

3.3. Antioxidant Effect

Tetracyclines also scavenge reactive oxygen species (ROS) and prevent oxidative damage to cell structures [29].

The phenolic ring is crucial for the ability of these compounds to retain ROS. Upon attachment of a free radical to the phenolic ring, a stable phenolic radical is formed which, surrounded by the side groups of the phenolic ring, does not undergo further interactions [30].

3.4. Anti-Apoptic Effect

Apoptosis is a tightly regulated programme of cell death. The initiating phenomenon of apoptosis involves the activation of caspases, which follows a hierarchical pattern in which higher-order caspases are activated by initial apoptotic signals and then cleave and activate lower-order caspases, which then carry out proteolysis. [31] Two pathways can lead to caspase activation.

The extrinsic pathway is triggered by the binding of death signal proteins to a receptor on the cell surface. This binding activates caspase-8, which then activates effector caspases.

The intrinsic pathway can be initiated by both intracellular and extracellular stimuli. It leads to an increase in mitochodnrial membrane permeability and release of cytochrome c into the cytoplasm. The formation of the apoptosome (a multiprotein composite formed by cytochrome c) activates caspase-9 initiating further caspase activation [29, 32].

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Also in the intrinsic pathway via the mitochondrial regulation inhibitor of SMAC and DIABLO, groups of proteins bind to the inhibitor of apoptosis proteins (IAP) and by inactivating them allow apoptosis to proceed. Another group of proteins, called apoptosis inducing factors (AIF), function in a caspase-independent pathway and cause DNA fragmentation inside the cell nucleus [33, 34, 35, 36].

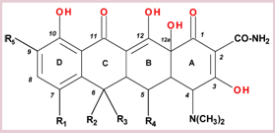
In vitro studies on animal models showed that tetracyclines caused a decrease in caspase expression [37]. The accumulation of tetracyclines in mitochondria was also demonstrated, as well as the possibility of altering the membrane potential, which interferes with the synthesis of proteins encoded by mitochondrial DNA. [32, 38] The inhibition of cytochrome c release is another proposed mechanism [32].

The most information on the anti-apoptotic properties of tetracyclines was obtained from studies of the properties of minocycline in psychiatric and neurodegenerative diseases.

A Total of 83% of all selected studies conducted on animal models presented positive results, however this percentage was much Lower in randomised clinical trias. It is mainly due to the different doses of the drug used in both types of studies, difficulty in selecting patients at the same stage of the disease. Furthermore, some of the symptoms of these diseases are impossible to reproduce in an animal model [39].

Such encouraging results from preclinical studies require further standardization and the improvement of clinical protocols in order to objectify the results.

Table 1. Characteristic of tetracycline group.

	Broad spectrum				Narrow spectrum
	1st generation	2nd generation			3rd generation
	Tetracycline	Doksycycline	Minocycline	Limecycline	Sarecycline
Chemical structure	tetracyclic naphthacene-carboxamide ring system and conventional numbering of the condensed rings and key positions. 				
	methyl and hydroxyl groups at C6 carbon	hydroxyl group at C5 carbon and methyl group at C6 carbon	dimethylamine group at carbon C7		aminomethyl group at the C7 carbon
Intake	mandatory meal interval	can be taken with food	can be taken with food	can be taken with food	can be taken with food

4.1. Tetracycline

Tetracycline is the first representative of the group. It is formed of four six-carbon rings with attached methyl and hydroxyl groups at the C6 carbon [40].

After oral administration it is rapidly absorbed from the digestive tract with the maximal concentration being reached after 1-3 hours. However, the absorption may be reduced in the presence of milk products or preparations including metal ions.

DOXYCYCLINE

Doxycycline consists of four identical six-carbon rings with an additional hydroxyl group at the C5 carbon and a methyl group at the C6 carbon. [41]

It was approved by the FDA in the treatment of severe forms of acne at the dose of 50-100 mg 1-2 times daily. [42]

As regards doxycycline, the effectiveness of the dose not including the bacteriostatic activity was precisely demonstrated, both in acne vulgaris and in acne rosacea.

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In Europe and the United States, doxycycline with exclusive anti-inflammatory activity is available at the dose of 40 mg, which includes 30 mg of immediate-release monohydrate and 10 mg in slow-release microgranule form. The preparation is entirely devoid of antibacterial activity. In 2006 it was approved by the FDA for the treatment of acne rosacea. [43]

Doxycycline at a dose of 20 mg was registered for the treatment of periodontal diseases in adults, and its efficacy in this indication was ascribed to the inhibiting activity of collagenase and matrix metalloproteinase. [44, 45]

Doxycycline is the first-line treatment in wide range of infections including *Treponema pallidum* (syphilis), *Borrelia burgdorferi, B. afzelii, B. garinii* (borreliosis), *Coxiella burnetii* (Q fever), *Rickettsia rickettsii* (Rocky Mountain spotted fever) and *Yersinia pestis* (plague) [46].

4.2. Lymecycline

Lymecycline is a semisynthetic tetracycline, developed by combining tetracycline with L-lysine. Compared to tetracycline it is characterized by higher absorption levels, enhanced tissue penetration, higher serum level, and slower elimination [47].

Due to the highest oral absorption of all tetracyclines [48] lymecycline is administered at Simple, once-daily regimen. It induces fewer adverse effects than previously used drugs from this group [49].

It is unavailable in North America.

A multicenter, randomized blinded study conducted to compare the efficacy, safety and cost-effectiveness of using lymecycline and minocycline revealed that both drugs had a similar safety and efficacy profile, while the cost of treatment with lymecycline was 4-fold lower [50, 51, 52].

4.3. Minocycline

Minocycline consists of a tetracyclic ring with an additional dimethyl amino group at the C7 carbon which makes it the most lipophilic tetracycline.

Due to this property it crosses the blood-brain barrier and reaches high concentrations in the central nervous system, which explains more frequent occurrence of adverse effects such as nausea, vomiting and vertigo. [53]

It was approved by the FDA in the treatment of severe acne at a dose of 50-135 mg/day.

When treatment is continued for more than 6 months it may cause characteristic pigmentation, lupus-like lesions and irritable bowel syndrome. [54, 55]

4.4. Sarecycline

Sarecycline is a new narrow-spectrum antibiotic with bacteriostatic activity. Similarly to the remaining tetracyclines it inhibits the synthesis of proteins by the disruption of the 30S subunit binding.

It was developed mainly for the treatment of acne lesions. It contains a tetracyclic ring which was modified by binding aminomethyl group at the C7 carbon [56].

Such a modification may be responsible for maintaining antibacterial activity against *Cutibacterium acnes* and decreasing the activity against bacteria which make up the intestinal microflora [56, 57]. Apart from bacteriostatic activity it inhibits neutrophil chemotaxis and the activity of extracellular matrix metalloproteinases.

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Table 2. The most common adverse effects of tetracycline antibiotics.

TETRACYCLINE	DOKSYCYCLINE	LIMECYCLINE	MINOCYCLINE	SARECYCLINE
•diarrhea •increased total bilirubin levels •abdominal pain •vaginal candidiasis •symptoms of increased intracranial pressure	•vaginal candidiasis •nausea •phototoxicity	•nausea •diarrhea •headache	•CNS-related manifestations (nausea, vomiting, vertigo) due to the lipophilic properties •at higher doses it may cause characteristic discolorations, lupus-like lesions and irritable bowel syndrome	•nausea, vomiting approx. 2%, diarrhea 1% • vertigo < 1%

5. Side effects on the skin or interractions with other medicines.

In this article, we focus on side effects that are of particular relevance to the daily work of a dermatologist - that is, those involving the skin or interactions with other drugs.

5.1. Phototoxicity

Tetracyclines usually trigger phototoxicity, but not photoallergy. The former is independent from immune response, so it may also occur during the first exposure to the drug. However, due to dose dependence phenomenon it occurs when the suitable amount of the drug is concentrated in the skin and it is exposed to suitable quantities of non-ionizing electromagnetic radiation.

UVA (320–400 nm) is a part of the solar spectrum which is most commonly considered as being related with phototoxicity. However, UVB (290–320 nm) and visible light may contribute to the development of such a reaction [58].

Clinically speaking, a phototoxic reaction resembles a severe excessive sunburn characterized by erythema, edema, occasional vesicles, and burning followed by exfoliation.

Depending on skin type and pigmentation, a reaction appears within several minutes or hours after exposure to light [59].

Older generations of tetracyclines were much more likely to trigger skin reactions. The family of tetracyclines includes numerous molecules. Not all of them induce significant phototoxic reactions. Until recently, the use of tetracyclines in summer had still been discussed. Research revealed a number of significant events ascribed to minocycline and lymecycline, while the majority of studies concerned doxycycline. There is a ten-

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dency towards the standardization of the family of tetracyclines to be defined as "photosensitizing drugs" without differentiating between various molecules.

5.2. HIPERPIGMENTATION

This adverse effect is characteristic of minocycline. It is induced by the precipitation of the minocycline-iron complex in the skin [60]. The incidence of discolorations induced by minocycline ranges from 2.4% to 41% and is the highest in patients with rheumatoid arthritis. Depending on the type, discolorations are located on the face within the inflammatory areas (type 1), on the healthy skin within the forearm and shin (type 2) or diffuse discolorations which affect sun-exposed skin (type 3 – the least common) [61].

5.3. Onycholysis, Fotoonycholysis

Both onycholysis and photoonycholysis have been described in the context of tetracyclines. They can affect both hands and feet, also with some nails spared. The more frequent involvement of the fingers than the feet, which are less commonly exposed, confirms a mechanism involving UV radiation.

The first case of photoonycholysis after limecycline was described in 2014. [62]

As regards doxycycline, onycholysis of the distal part of the nail plate and nail discolouration occur at a frequency of less than 1:1000 [63]

5.4. Induced Lupus Erythematosus

An important and possible consequence of tetracycline use is the development of systemic lupus. It May be trigerred by the use of older generation tetracyclines, but is most commonly described in relation to minocycline.

Approximately 57 cases of minocycline induced lupus have been fully reported to date. Arthritis was the presenting symptom in 100% of patients. It involved small and large joints of the upper and lower limbs. Skin lesions were observed in about 1/5 of patients, with the typical lupus-like butterfly-shaped erythema or discoid rash [64] affecting only 1 patient [65].

Tests such as antibodies to DNA, antihistones or anti-Sm antibodies seem to be less sensitive to minocycline-induced lupus.

5.5. IDIOPATHIC INTRACRANIAL HYPERTENSION

One of the more dangerous side effects of tetracyclines is the possibility of increased intracranial pressure. The symptom complex also described by the synonym „pseudotumor cerebri" is manifested by a headache, tinnitus synchronous with pulse and transient visual disturbances. The headache involves the frontal region, is most severe shortly after awakening and worsens when lying down. [66]

According to the latest systematic review conducted in 2019, the highest category V of drugs that may cause intracranial hypertension include tetracyclines, vitamin A and its derivatives (including isotretinoin and tretinoin) and recombinant growth hormone [67].

The pathophysiology of intracranial hypertension is not fully elucidated. It is likely that tetracyclines reduce cerebrospinal fluid outflow through the arachnoid villi, and that the metabolites of oral retinoids (retinols) have a direct toxic effect on them [68, 69].

6. The use of tetracyclines in the treatment of infectious dermatological diseases.

In everyday dermatological practice, acne is often treated with a combination of oral antibiotics and oral retinoids. However, as tetracyclines and isotretinoin belong to the high-risk category of hypertension, concomitant use of these drugs is not recommended.

Although all tetracyclines are structurally similar, they differ significantly in their antimicrobial activity and range of side effects, which affects their clinical application.

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Table 3. Bacteriostatic activity of tetracyclines – use in infectious diseases.

Indication	Dosage	Comment	Refferences
Early Lyme borreliosis	Erythema migrans 2 x 100 mg 14-21 days p.o. Borrelial lymphoma 2 x 100 mg 14-28 days p.o. Early neuroborreliosis 2 x 100 mg 14-28 days p.o. Lyme carditis 2 x 100 mg 14-30 days p.o. Lyme arthritis 2 x 100 mg 14-28 days p.o.	Dosage recommended in any form of early borreliosis, including erythema migrans, borrelial lymphoma, early neuroborreliosis, Lyme carditis, Lyme arthritis	[1]
Late Lyme borreliosis	Lyme arthritis 2 x 100 mg 28 days p.o./i.v. Acrodermatitis chronica atrophicans 2 x 100 mg 14-21 days p.o.	Doxycycline is not used in late neuroborreliosis	
Early syphilis	Doxycycline 2 x 100 mg 14 days p.o.	It is alternative treatment in case of allergy to penicillin	[2]
Late syphilis	Doxycycline 2 x 100 mg 28 days p.o.	It is alternative treatment	
Rickettsioses	Doxycycline 2 x 100 mg for at least 10 days	The group of rickettsioses includes: - Spotted fever group (Rocky Mountain spotted fever, Mediterranean spotted fever, African tick bite fever, varicelliform rickettsial disease) - Typhus group (murine, endemic, epidemic, bush typhus) - Q fever	[3]
Nongonococcal urethritis caused by chlamydia	Doxycycline 100 mg p.o. twice a day for 7days (first line treatment)		[4]
Lymphogranuloma venereum caused by *Chlamydia trachomatis*	100 mg twice daily for 21 days, p.o. (first Line treatment)		[5]
Granuloma inguinale caused by *Klebsiella granulomatis*	Doxycycline 100mg bd p.o., Duration of treatment should be for at least three weeks or until complete healing is achieved. (secodnd line treatment)		[6]

7. The use of tetracyclines in the treatment of non-infectious dermatological diseases.

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Table 4. Non-antibiotic activity of tetracyclines – use in inflammatory diseases.

	Mechanism of action	Recommended dosage pattern	Mechanism of action – references
Acne	Inhibition of neutrophil chemotaxis induced by *P. acnes* Inhibition of IL-8 (a chemotactic cytokine and activator of neutrophils) Inhibition of MMP Reactive oxygen species scavenging Inhibition of phospholipase A2	Tetracycline: 1 g daily given in divided doses; when improvement occurs in 1-2 weeks, decrease slowly to a maintenance dosage of 125-500 mg daily Doxycycline: 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg/Day Minocycline: 50 mg 1-3 times daily Limecycline: 300mg once daily for 12 weeks	[1, 2, 3]
Rosacea	Inhibition of the activation and degranulation of neutrophils Suppression of pro-inflammatory cytokines TNFα and IL-1β Decreasing the levels of MMP (especially MMP 9) Inhibition of the expression of nitric oxide synthase	Tetracycline 250-500mg twice daily for 4-8 weeks p.o. Doxycycline 50-100mg once or twice daily for 4-8 weeks p.o.	[4]
Autoimmune bullous disorder	Inhibition of MMP activity Inhibition of mast cell activation	Doxycycline 2x200mg	[5]
Neutrophilic disorders: Pyoderma gangrenosum Sweet's syndrome Neutrophilic dermatosis of the dorsal hands	Inhibition of IL-8 and neutrophil activation	1,5-2 g daily given in divided doses p.o.	[6, 7]
Granulomatous diseases: Sarcoidosis Necrobiosis lipoidica	Inhibition of granuloma formation *in vitro*	1,5-2 g daily given in divided doses p.o.	[8]
Aphtosis, periodontitis	Inhibition of MMP	Doxycycline 20mg p.o. Tetracycline (250 mg) used as a mouth rinse and subsequently swallowed	[9, 10]
Palmoplantar pustular psoriasis	Due to limited data the exact	Tetracycline 250mg, twice daily p.o.	[11]

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	mechanism has not been clear		
Hidradenitis suppurativa	Inhibition of proinflammatory cytokine levels Inhibition of the activation and degranulation of neutrophils scavenge reactive oxygen species (ROS)	Tetracycline 500mg twice daily for 4 months p.o.	[12]

Based on our own experience and the latest literature, below we explain the use of tetracyclines in several skin diseases which are hard to treat.

7.1. Granulomatous Diseases: Necrobiosis Lipoidica, Sarcoidosis

The use of doxycycline led to spectacular improvement in the treatment of granulomatous diseases over the past decade. Researchers published case reports concerning necrobiosis lipoidica and dermal forms of sarcoidosis [70, 71].

The effectiveness of doxycycline even in the ulcerative forms of necrobiosis lipoidica is most probably associated with its anti-inflammatory activity and the inhibition of tissue remodeling through the influence on metalloproteinases [70, 72].

Moreover, *in vitro* research showed that doxycycline inhibited the formation of granulation tissue via inhibiting protein kinase C [72, 73].

7.2. PRURIGO PIGMENTOSA

The clinical presentation of this dermatosis includes itchy brownish-erythematous papules which are mostly located in the upper part of the trunk. Reticulate hyperpigmentation is frequently observed within the exanthems. Skin lesions are accompanied by persistent pruritus [74]. The condition was first described by Nagashima in 1971 [75]. Currently, it is more and more commonly observed in patients consuming the ketogenic diet. It is often misdiagnosed with eczema. No improvement is often seen after the use of topical glucocorticosteroids. According to the authors of the case reports, immediate improvement occurred after introducing doxycycline/minocycline and resuming the consumption of complex carbohydrates, while diet modification itself brought no expected improvement [74, 75, 76].

7.3. Hidradenitis Suppurativa

Hidradenitis suppurativa/acne inversa (HS) is a chronic inflammatory skin disease characterized by painful, recurrent nodules and abscesses that rupture and lead to the formation of sinus tracts and sparring [77].

Its typical localizations are body folds, most commonly the axillae, inguinal and anogenital regions, but may affect other areas as well [78, 79].

The key factor in the pathogenesis of the lesions is follicular hyperkeratosis leading to follicular occlusion. As a result of closing the follicle outlet, epidermal cells, hair elements, sebum and bacteria accumulate. Clinically, blackheads and pustules are observed at this stage, where bacterial superinfection is a secondary phenomenon. The overcrowding of the hair follicle leads to its rupture, accompanied by inflammation resembling a foreign body reaction with neutrophilic infiltration. At further stages, the contents of the follicle seek an outlet which leads to the formation of fistulas. The healing process of such a massive inflammation leads to the fibrosis of the skin and subcutaneous tissue and the formation of sternal scars [80, 81, 82].

According to European guidelines for hidradenitis suppurativa published in 2016 oral antibiotics are the first line of treatment. Tetracyclines were recommended for less

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severe cases (Hurley I-II) and the combination of clindamycin and rifampicin - for the failure of first treatment or more advanced stages (Hurley II-III) [77].

In recent years, there has been much controversy regarding the long-term use of clindamycin and rifampicin. The contribution of clindamycin to therapeutic success remains questionable since rifampicin, as a known CYP3A4 inducer, was shown to reduce clindamycin blood levels by 90% [83].

It wa speculated that the consequent lower clindamycin levels in combination protocols might reduce the strength of the treatment itself in cases of severe HS lesions, as draining tunnels were commonly colonized by polymorph-abundant anaerobic microflora [84].

Prolonged and not fully effective antibiotic therapy leads to the selection of resistant strains and increases the risk of adverse reactions.

Considering the pathogenesis of hidradenitis suppurativa, where bacterial superinfection is a secondary process and neutrophils are the main cells in the inflammatory infiltrate, it is worth considering the use of tetracyclines not only at the early stages. A prospective, international cohort study including 283 patients showed similar efficacy of tetracyclines and a combination of rifampicin and clindamycin after 12 weeks of treatment, independent of the stage of the disease [85].

8. Summary

Tetracyclines are an ever-expanding group of antibiotics long used in dermatology. The pleiotropic effect is responsible for the efficacy of tetracyclines in infectious diseases as well as in inflammatory dermatoses. In the near future, the planned clinical trials evaluating the therapeutic activity of tetracyclines based on their concentration in plasma or tissues will be the basis for rationalization of dosage and duration of treatment in specific dermatological indications.

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References

1. Duggar, B.M. Aureomycin: a product of the continuing search for new antibiotics. *Ann. NY. Acad. Sci.* **1948**, 51, 177–81.

2. Ian, Ch.; Marilyn, R. Tetracycline Antibiotics: Mode of Action, Applications, Molecular Biology, and Epidemiology of Bacterial Resistance. *Microbiol. Mol. Biol. Rev.* **2001**, 65, 232–60.

3. Zakeri, B. W. G. Chemical biology of tetracycline antibiotics. *Biochem. Cell Biol.* **2008**, 86, 124-36.

4. Stephens, C. R.; Conover, L. H.; Pasternack, R.; Hochstein, F. A.; Moreland, W. T.; Regna, P. P. The structure of aureomycin. *J. Am. Chem. Soc.* **1954**, 76, 3568-75.

5. Golub, L.M.; Suomalainen, K.; Sorsa, T. Host modulation with tetracyclines and their chemically modified analogues. *Curr Opin Dent* **1992**, 2, 80-90.

6. Nelson, M.L. Chemical and biological dynamics of tetracyclines. *Adv Dent Res* **1998**, 12, 5-11.

7. Livermore DM. Antibiotic uptake and transport by bacteria. *Scand J Infect Dis Suppl*. **1990**, 74, 15-22.

8. White, J.R.; Pearce, F.L. Characterization of chlortetracycline (aureomycin) as a calcium ionophore. *Biochemistry* **1982,** 21, 6309–12.
9. Nelson, M.L.; Park, B.H.; Andrews, J.S.; Georgian, V.A.; Thomas, R.C.; Levy, S.B. Inhibition of the tetracycline efflux antiport protein by 13-thio-substituted 5-hydroxy-6-deoxytetracyclines. *J Med Chem*. **1993**, 36(3), 370-377.
10. Golub, L.M.; Ramamurthy, N.S.; McNamara T.F.; Greenwald, R.A.; Rifkin, B.R. Tetracyclines inhibit connective tissue breakdown: new therapeutic implications for an old family of drugs.*Crit Rev Oral Biol Med* **1991,** 2, 297–321.
11. Ryan, M.E.; Usman, A.; Ramamurthy, N.S.; Golub, L.M.; Greenwald, R.A. Excessive matrix metalloproteinase activity in diabetes: inhibition bytetracycline analogues with zinc reactivity. *Curr Med Chem* **2001,** 8, 305–316.
12. Stezowski, J.J. *J. Am. Chem. Soc.* **1975,** 98, 6012–6018.
13. Lambs, L.; Révérend, B.D.-L.; Kozlowski, H.; Berthon, G.; *Inorg. Chem.* **1988,** 27, 3001–3012.
14. Stezowski, J.J.; Pewo R., *J. Am. Chem. Soc.* **1977,** 99, 1117–1121
15. Neuvonen, P. J. Interactions with the absorption of tetracyclines. *Drugs* **1976**, 11, 45−54.
16. Weinstein, L.; Goodman, L. S.; Gilman, A.; *The Tetracyclines. In The Pharmacological Basis of Therapeutics*, 4th ed., The Macmillan Co.: New York, USA, 1970; 1253−1268.
17. Alexey, A.; Thomas, S. The Tetracycline:Mg2+ Complex: A Molecular Mechanics force *Field. J. Comput.Chem*. **2006**, 27, 1517–33.
18. Guerra, W.; Silva-Caldeira, P.; Terenzi, H.; Pereira-Maia, E.; Impact of metal coordination on the antibiotic and non-antibiotic activities of tetracycline-based drugs, *Coordination Chemistry Reviews* **2016**, 327–328, 188-199.
19. Del Ross J.Q.; Webster G.F.; Rosen T. Status report from the scientific panel on antiobiotic use in dermatology of the American Acne and Rosacea Society:part 1: antiobiotic prescribing patterns, sources of antibiotic exposure, antibiotic consumption and emergence of antibiotic resistance, impast of alterations in antibiotic prescribing, and clinical sequelae of antibiotic use. *J Clin Aesthet Dermatol.* **2016**, 9, 4, 18.
20. Golub, L.M.; Lee, H.M.; Ryan, M.E. Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. *Adv. Dent. Res.* **1998**, 12, 12–26.
21. Arvelo, F.; Cotte, C. Metalloproteinases in tumor progression. *Review. Invest. Clin.* **2006**, 47, 185-205.
22. Griffin, M. O., Ceballos, G., & Villarreal, F. J. Tetracycline compounds with non-antimicrobial organ protective properties: possible mechanisms of action. *Pharmacological research* **2011**, *63*, 2, 102–107.
23. Roy, S.K.; Kendrick, D.; Sadowitz, B.D.; Gatto, L.; Snyder, K.; Satalin, J.M. Jack of all trades: Pleiotropy and the application of chemically modified tetracycline-3 in sepsis and the acute respiratory distress syndrome (ARDS). *Pharmacol Res* **2011**, 64, 580-9.
24. Khanapure, S. P.; Garvey, D. S.; Janero, D. R.; Letts, L. G. Eicosanoids in inflammation: biosynthesis, pharmacology, and therapeutic frontiers. *Curr. Top. Med. Chem.* **2007**, 7, 311-40.
25. Bahrami F, Morris DL, Pourgholami MH. Tetracyclines: drugs with huge therapeutic potential. Mini Rev. Med. Chem. 2012; 12: 44–52.
26. Webster, G.; Del Rosso, J.Q. Anti-inflammatory activity of tetracyclines. *Dermatol. Clin.* **2007**, 25, 133–5.
27. Goodheart, G.L. Further evidence of the role of bivalent cations in leukocyte chemotaxis. *J. Reticuloendothel. Soc.* **1979,** 25, 545–54.
28. Trachtman, H.; Futterweit, S.; Greenwald, R.; Moak, S.; Singhal, P.; Franki, N. Chemically modified tetracyclines inhibit inducible nitric oxide synthase expression and nitric oxide production in cultured rat mesangial cells. *Biochem Biophys Res Commun* **1996**, 229, 243-8.

29. Griffin, M.O.; Fricovsky, E.; Ceballos, G.; Villarreal, F. Tetracyclines: a pleitropic family of compounds with promising therapeutic properties. Review of the literature. *Am J Physiol.* **2010,** 299, C539-C548.
30. Kraus, R.L., Pasieczny, R.; Lariosa-Willingham, K.; Turner, M.S.; Jiang, A.; Trauger, J.W. Antioxidant properties of minocycline: neuroprotectionin an oxidative stress assay and direct radical-scavenging activity. *JNeurochem* **2005,** 94, 819–827.

31. Cryns, V.; Yuan, J. Proteases to die for [published correction appears in Genes Dev 1999 Feb 1;13(3):371]. *Genes Dev*. **1998**, 12, 11, 1551-1570.
32. Sagar, J.; Sales, K.; Seifalian, A.; Winslet, M. Doxycycline in mitochondrial mediated pathway of apoptosis: a systematic review. *Anti-Cancer Agents Med. Chem.* **2010**, 10, 556–563.
33. de Almagro, M.C.; Vucic, D. The inhibitor of apoptosis (IAP) proteins are critical regulators of signaling pathways and targets for anti-cancer therapy. *Exp. Oncol.* **2012;** 34, 200–211.
34. Garrido, C.; Galluzzi, L.; Brunet, M.; Puig, P.E.; Didelot, C.; Kroemer, G. Mechanisms of cytochrome c release from mitochondria. *Cell Death Differ.* **2006,** 13, 1423–1433.
35. Susin, S.A.; Lorenzo, H.K.; Zamzami, N.; Marzo, I.; Snow, B.E.; Brothers, G.M.; Molecular characterization of mitochondrial apoptosis-inducing factor. *Nature* **1999,** 397, 441–446.
36. Joza, N.; Susin, S.A.; Daugas E.; Stanford, W.L.; Cho, S.K.; Li, C.Y. Essential role of the mitochondrial apoptosis-inducing factor in programmed cell death. *Nature* **2001,** 410, 549–554.
37. Chen, M.; Ona, V. O.; Li, M.; Ferrante, R. J.; Fink, K. B.; Zhu, S.; Bian, J.; Guo, L.; Farrell, L. A.; Hersch, S. M.; Hobbs, W.; Vonsattel, J. P.; Cha, J. H.; Friedlander, R. M. Minocycline inhibits caspase-1 and caspase-3 expression and delays mortality in a transgenic mouse model of Huntington disease. *Nat. Med.* **2000**, 6, 797–801.
38. Riesbeck, K.; Bredberg, A.; Forsgren, A. Ciprofloxacin does not inhibit mitochondrial functions but other antibiotics do. Antimicrob. *Agents Chemother*. **1990**, 34, 167–169.
39. Romero-Miguel, D.; Lamanna-Rama, N.; Casquero-Veiga, M.; Gómez-Rangel, V.; Desco, M.; Soto-Montenegro, M.L.; Minocycline in neurodegenerative and psychiatric diseases: An update. *Eur J Neurol*. **2021,** 28(3), 1056-1081.
40. Mitscher, L. A. The *chemistry of the tetracycline antibiotics.* Marcel Dekker , New York, NY, USA, 1978.
41. Barza, M.; Brown, R.B.; Shanks, C.; Gamble, C.; Weinstein, L. Relation between lipophilicity and pharmacological behavior of minocycline, doxycycline, tetracycline, and oxytetracycline in dogs. *Antimicrob Agents Chemother.* **1975**, 8, 713-720.
42. Thiboutot, D.; Gollnick, H.; Bettoli, V.; New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. *J. Am. Acad. Dermatol*. **2009**, 60, 1–50.
43. Di Caprio, R.; Lembo, S.; Di Costanzo, L.; Balato, A.; Monfrecola, G.; Anti-inflammatory properties of low and high doxycycline doses: an in vitro study. *Mediators Inflamm*. **2015**, 329418.
44. Sorsa, T.; Tjäderhane, L.; Konttinen, Y.T.; Matrix metalloproteinases: contribution to pathogenesis, diagnosis and treatment of periodontal inflammation. *Ann Med*. **2006**, 38(5), 306-321.
45. Gomis-Rüth, F.X. Third time lucky? Getting a grip on matrix metalloproteinases. *J Biol Chem*. **2017**, 292(43), 17975-17976.
46. Hoyt, J. C.; Ballering, J.; Numanami, H.; Hayden, J. M.; Robbins, R. A. Doxycycline modulates nitric oxide production in murine lung epithelial cells. J. Immunol. 2006, 176, 567–572.
47. Cunliffe, W.J.; Meynadier, J.; Alirezai, M. Is combined oral and topical therapy better than oral therapy alone in patients with moderate to moderately severe acne vulgaris? A comparison of the efficacy and safety of lymecycline plus adapalene gel 0.1%, versus lymecycline plus gel vehicle. *J Am Acad Dermatol*. **2003**, 49, 3, 218-226.

 doi:10.20944/preprints202205.0056.v1

48. Chen, Y.; Wu, J.; Yan, H.; Lymecycline reverses acquired EGFR-TKI resistance in non-small-cell lung cancer by targeting GRB2. *Pharmacol Res*. **2020**, 159, 105007.
49. Maglie, R.; Quintarelli, L.; Caproni, M.; Antiga, E. Impressive response of erosive pustular dermatosis of the scalp to lymecycline monotherapy. *J Dtsch Dermatol Ges.* **2019**, 17(11), 1177-1178.
50. Bossuyt L, Bosschaert J, Richert B, Cromphaut P, Mitchell T, Al Abadie M, Henry I, Bewley A, Poyner T, Mann N, Czernielewski J. Lymecycline in the treatment of acne: an efficacious, safe and cost-effective alternative to minocycline. Eur J Dermatol. 2003 Mar-Apr;13(2):130-5.
51. Grosshans E, Belaïch S, Meynadier J, Alirezai M, Thomas L. A comparison of the efficacy and safety of lymecycline and minocycline in patients with moderately severe acne vulgaris. Eur J Dermatol. 1998 Apr-May;8(3):161-6.
52. Ocampo-Candiani, J.; Velazquez-Arenas, L.L.; de la Fuente-Garcia, A.; Trevino-Gomezharper, C.; Berber, A. Safety and efficacy comparison of minocycline microgranules vs lymecycline in the treatment of mild to moderate acne: randomized, evaluator-blinded, parallel, and prospective clinical trial for 8 weeks. *J Drugs Dermatol.* **2014**, 13(6), 671-6.
53. Zhanel, G.G.; Homenuik, K.; Nichol, K. The glycylcyclines: a comparative review with the tetracyclines. Drugs 2004; 64 (1): 63-88
54. Griffin, M.O.; Ceballos, G.; Villarreal, F.J. Tetracycline compounds with non-antimicrobial organ protective properties: possible mechanisms of action. *Pharmacol Res* **2011**, 63, 102–107.
55. Garrido-Mesa, N.; Zarzuelo, A.; Galvez, J. Minocycline: far beyond an antibiotic. *Br J Pharmacol* **2013**, 169, 337–352.
56. Zhanel, G.; Critchley, I.; Lin, L.Y.; Alvandi, N. Microbiological Profile of Sarecycline, a Novel Targeted Spectrum Tetracycline for the Treatment of Acne Vulgaris. *Antimicrob Agents Chemother.* **2018**, 21, 63(1):e01297-18.
57. Kaul, G.; Saxena, D.; Dasgupta, A.; Chopra, S. Sarecycline hydrochloride for the treatment of acne vulgaris. *Drugs Today* **2019**, 55(10), 615-625. 58. Lee, A.; Thomson, J. *Drug-induced skin reactions.* 2nd ed. London: Pharmaceutical Press; 2006: 125-156.
59.Odorici, G.; Monfrecola, G.; Bettoli, V. Tetracyclines and photosensitive skin reactions: A narrative review. *Dermatol Ther*. **2021**, 34(4):e14978.
60. Gordon G.; Sparano, B.M.; Iatropoulos, M.J. *Arch. Dermatol.* **1985**, 121, 618–623.
61. Abdelghany, M.; Kivitz, A.J. Minocycline-induced hyperpigmentation. *Cleve Clin J Med.* **2016**, 83(12), 876-877.
62. Wlodek, C.; Narayan, S. A reminder about photo-onycholysis induced by tetracycline, and the first report of a case induced by lymecycline. *Clin Exp Dermatol.* **2014,** 39(6), 746-7.
63. Czap, C.; Weckopp, S. Distal Phototoxic Onycholysis. *Dtsch Arztebl Int.* **2020**, 20, 117(12), 196.
64. Tan, E.M.; Cohen, A.S.; Fries, J.F.; Masi, A.T.; McShane, D.J.; Rothfield, N.F.; Schaller, J.G.; Talal, N.; Winchester, R.J.; The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* **1982**, 25, 1271–1277.
65. Schlienger, R.G.; Bircher, A.J.; Meier, C. R. Minocycline-Induced Lupus . *Dermatology* **2000,** 200, 223-231.
66. Wall, M. Update on Idiopathic Intracranial Hypertension. *Neurol Clin*. **2017**, 35(1),45-57.
67. Tan, M.G.; Worley, B.; Kim, W.B.; Ten Hove, M.; Beecker, J. Drug-Induced Intracranial Hypertension: A Systematic Review and Critical Assessment of Drug-Induced Causes. *Am J Clin Dermatol*. **2020**, 21(2), 163-172.
68. Bababeygy, S.R.; Repka, M.X.; Subramanian, P.S. Minocycline-associated pseudotumor cerebri with severe papilledema.*J Ophthalmol*. **2009**, 203583.
69. Warner, J.E.; Bernstein, P.S.; Yemelyanov, A.; Alder, S.C.; Farnsworth, S.T.; Digre, K.B. Vitamin A in the cerebrospinal fluid of patients with and without idiopathic intracranial hypertension. *Ann Neurol.* **2002,** 52(5), 647-650.

70. Perret, L. J.; Tait, C. P. Non-antibiotic properties of tetracyclines and their clinical application in dermatology. *Australasian Journal of Dermatology* **2014,** 55(2), 111-118.
71. Blevins, M. Atypical Ulcerative Necrobiosis Lipoidica Diabeticorum: A Case Study. *The International Journal of Lower Extremity Wounds*. **2021**. 72. Duarte, A.; Mota, A.; Pereira, M.; Baudrier, T.; Azevedo F. Generalized granuloma annulare - response to doxycycline. *J Eur Acad Dermatol Venereol.* **2009**, 23(1), 84-85.
73.Burns, E.; Ukoha, U.; Chan, A. Necrobiosis lipoidica with rapid response to doxycycline. *Pediatr Dermatol.* **2020**, 37(5), 981-982.
74. Mumford, B.P.; Lasocki, A. Prurigo pigmentosa: the "keto rash". *Med J Aust.* **2021**, 2, 215(3), 108-108.e1.
75. Nagashima, M. Prurigo pigmentosa-clinical observations of our 14 cases. *J Dermatol.* **1978**, 5(2), 61-7.
76. Lu, L.Y.; Chen, C.B. Keto Rash: Ketoacidosis-Induced Prurigo Pigmentosa. *Mayo Clin Proc.* **2022,** 97(1), 20-21. doi: 10.1016/j.mayocp.2021.11.019. PMID: 34996560.
77. Gulliver, W.; Zouboulis, C.C.; Prens, E.; Jemec, G.B.; Tzellos, T. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. *Rev Endocr Metab Disord*. **2016**, 17(3), 343-351.
78. Fimmel, S.; Zouboulis, C.C. Comorbidities of hidradenitis suppurativa (acne inversa) *Dermatoendocrinol.* **2010**, 2, 9–16.
79. Kurzen, H.; Kurokawa, I.; Jemec, G.B.; What causes hidradenitis suppurativa? *Exp Dermatol.* 2008, 17, 455–472.
80. Yu, C.C.; Cook, M.G. Hidradenitis suppurativa: a disease of follicular epithelium, rather than apocrine glands. *Br J Dermatol* **1990**, 122, 763-9.
81. Jemec, G.B.; Hansen, U. Histology of hidradenitis suppurativa. *J Am Acad Dermatol* **1996**, 34, 994-9.
82. Kamp, S.; Fiehn, A.M.; Stenderup, K. Hidradenitis suppurativa: a disease of the absent sebaceous gland? Sebaceous gland number and volume are significantly reduced in uninvolved hair follicles from patients with hidradenitis suppurativa. *Br J Dermatol* **2011**, 164, 1017-22.
83. Albrecht, J.; Baine, P.A.; Ladizinski, B.; Jemec, G.B.; Bigby, M. Long-term clinical safety of clindamycin and rifampicin combination for the treatment of hidradenitis suppurativa. A Critically Appraised Topic. *Br J Dermatol***. 2019,** 180(4), 749-755.
84. Join-Lambert, O.; Guet-Revillet, H.; Lecuyer, H. *The Microbiology of Hidradenitis Suppurativa.* Chicago, IL: ICAAC; 2011.
85. van Straalen, K.R.; Tzellos, T.; Guillem, P. The efficacy and tolerability of tetracyclines and clindamycin plus rifampicin for the treatment of hidradenitis suppurativa: Results of a prospective European cohort study. *J Am Acad Dermatol*. **2021**, 85(2), 369-378.

Refferences Tab. 3

1. Lantos P.M.; Rumbaugh J.; Bockenstedt L.K.. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis, and Treatment of Lyme Disease. *Arthritis Rheumatol*. **2021**, 73, 1, 12-20.
2. Janier, M.; Unemo, M.; Dupin, N.; Tiplica, G. S.; Potočnik, M., Patel, R. 2020 European guideline on the management of syphilis. *Journal of the European Academy of Dermatology and Venereology* **2021**, *35*, 3, 574–588.

3. Fralish M.S.; Mangalindan K.E.; Farris C.M.; Jiang J.; Green M.C.; Blaylock J.M. African Tick-Bite Fever. *Am J Med.* **2020**, 133, 9, 1051-1053
4. Lanjouw E.; Ouburg S.; de Vries H. J.; Stary A.; Radcliffe K.; Unemo M. European guideline on the management of Chlamydia trachomatis infections. *Int J STD AIDS*. **2016**, 27, 5, 333-348.
5. de Vries H.J.C.; de Barbeyrac B.; de Vrieze N.H.N. European guideline on the management of lymphogranuloma venereum. *J Eur Acad Dermatol Venereol*. **2019**, 33, 10, 1821-1828.
6. O'Farrell N., Moi H. European guideline on donovanosis. *Int J STD AIDS*. **2016**, 27, 8, 605-607.

Refferences Tab. 4

1. Garcia-Martinez E.; Sanz-Blasco S.; Karachitos A. Mitochondria and calcium flux as targets of neuroprotection caused by minocycline in cerebellar granule cells. *Biochemistry* **2010**, 79, 239–50.
2. Sapadin A.N.; Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol*. **2006**, 54, 2, 258-265.
3. Zaenglein A.L.; Pathy A.L.; Schlosser B.J. Guidelines of care for the management of acne vulgaris [published correction appears in J Am Acad Dermatol. **2020**, 82, 6, 1576 *J Am Acad Dermatol*. **2016**, 74, 5, 945-73.
4. Amin A.R.; Patel R.N.; Thakker G.D. Post-transcriptional regulation of inducible nitric oxide synthase mRNA in murine macrophages by doxycycline and chemically modified tetracyclines. *FEBS Lett.* **1997**, 410, 259–64.
5. Monk E.; Shalita A.; Siegel D.M. Clinical applications of nonantimicrobial tetracyclines in dermatology. *Pharm. Res.* **2011**, 63, 130–45.

6. Joshi R.K.; Atukorala D.N.; Abanmi A. Successful treatment of Sweet's syndrome with doxycycline. *Br. J. Dermatol*. **1993**, 128, 584–6.

7.Berth-Jones J.; Tan S.V.; Graham-Brown R.A.C. The successful use of minocycline in pyoderma gangrenosum – a report of seven cases and review of the literature. *J. Dermatol. Treatment* **1989,** 1, 23–5.

8. Webster G.F.; Toso S.M.; Hegemann L.R. Inhibition of in vitro granuloma formation by tetracyclines and ciprofloxacin: involvement of protein kinase C. *Arch. Dermatol.* **1994**, 130, 748–52.

9. Peterson J.T.; Matrix metalloproteinase inhibitor development and the remodeling of drug discovery. *Heart Fail. Rev.* **2004**, 9, 63–79.

10. Kennedy R.; Alibhai M.; Shakib K. Tetracycline: a cure all? *Br J Oral Maxillofac Surg*. **2014**, 52, 4, 382-3.

11. Marsland, A. M., Griffiths, C. E. Treatments for chronic palmoplantar pustular psoriasis. *Skin therapy letter*, **2001**, *6*, 12, 3-5.

12. Gulliver W.; Zouboulis C.C.; Prens E.; Jemec G.B.; Tzellos T. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. *Rev Endocr Metab Disord*. **2016**, 17, 3, 343-351.