A RATIONAL PHARMACOTHERAPEUTIC STUDY IN PHARMACOVIGILANCE: A COMPARATIVE ASSESSMENT OF SAFETY BETWEEN TOPICAL 1% NADIFLOXACIN AND 0.1% ADAPALENE COMBINATION THERAPY AND TOPICAL 1% NADIFLOXACIN AND 0.025% TRETINOIN COMBINATION THERAPY, IN MILD TO MODERATE ACNE, IN TERTIARY CARE HOSPITALS, IN INDIA

Moumita Hazra[1]

[1]*Assistant Professor, Department of Pharmacology, K. D. Medical College, Hospital and Research Centre, Mathura, Uttar Pradesh.*

ABSTRACT

BACKGROUND

Topical adapalene and tretinoin, are comedolytic, anti-comedogenic and anti-inflammatory, on RAR (α, β, γ) receptors binding. Due to higher chemical stability, lipophilicity and lesser photo-lability, adapalene enables quicker follicular penetration, by lesser anti-AP-1 (c-Jun, c-Fos) and no CRBPII mRNA action, thus producing lesser photosensitivity and no skin irritation, unlike tretinoin; in which, these are reducible by overnight application, combination therapy, slow-release polymers or emollients. Topical nadifloxacin is bactericidal, anti-inflammatory and comedolytic, with inhibitory effect on DNA gyrase, DNA topoisomerase IV and IL-1α, IL-6, IL-8. The Global Alliance to Improve Outcomes in Acne guidelines recommend synergistic and additive combination therapies, which enhance therapeutic efficacy and reduce adverse effects. Due to inadequacy of data, this study was conducted, to compare the safety between topical 1% nadifloxacin and 0.1% adapalene combination therapy and topical 1% nadifloxacin and 0.025% tretinoin combination therapy, in mild to moderate acne, in tertiary care hospitals, in India.

METHODS

Groups A and B (50 patients each), applied topical 1% nadifloxacin and 0.1% adapalene combination therapy and 1% nadifloxacin and 0.025% tretinoin combination therapy, respectively, over their mild to moderate facial acne lesions, once daily overnight; and adverse effects, like erythema, scaling, dryness, pruritus, burning or stinging, were assessed on 0, 15, 30, 60, 90 days and follow-ups, by Local Irritation Scale. This is a multi-centre, prospective, randomised, open-labelled, comparative, rational pharmacotherapeutic study. Data was statistically analysed, with the calculation of Z values and p values, along with the Z test for proportions.

RESULTS

In both groups, no adverse effects were observed, with no statistically significant difference among the observations.

CONCLUSIONS

The therapies were well tolerated and safe among both groups.

KEYWORDS

Nadifloxacin, Adapalene, Tretinoin, Acne Vulgaris, Safety, Local Irritation Scale

HOW TO CITE THIS ARTICLE: Hazra M. A rational pharmacotherapeutic study in pharmacovigilance: a comparative assessment of safety between topical 1% nadifloxacin and 0.1% adapalene combination therapy and topical 1% nadifloxacin and 0.025% tretinoin combination therapy, in mild to moderate acne, in tertiary care hospitals, in India. J. Evid. Based Med. Healthc. 2019; 6(35), 2366-2371. DOI: 10.18410/jebmh/2019/484

BACKGROUND

Acne vulgaris is a self-limited, chronic inflammatory disease of the pilosebaceous unit, which causes cosmetic impairment.[1,2,3,4] The Global Alliance to Improve Outcomes in Acne guidelines recommend a combination therapy with a topical retinoid and antimicrobial agents for the treatment of mild to moderately severe inflammatory acne.[5,6,7,8]

Adapalene and tretinoin, the retinoids, are natural or synthetic derivatives of vitamin-A, and are comedolytic, anti-comedogenic, anti-inflammatory and reduce Propionibacterium acnes counts.[9,10,11,12] In monotherapy or combination therapy, its ability to stimulate the growth of new cells, unclog pores and promote the normal flow of sebum is well proven. Adapalene and tretinoin have selective affinity for retinoid receptors, including retinoic acid receptors (RAR) α, β and γ, affecting cellular differentiation and proliferation. Upon binding to tretinoin, these RAR receptors form heterodimers, which subsequently bind specific DNA sequences, called retinoic acid-responsive elements (RARE), that activate transcription of genes, whose products produce the desirable pharmacological effects of

Financial or Other, Competing Interest: None.
Submission 21-08-2019, Peer Review 23-08-2019,
Acceptance 28-08-2019, Published 02-09-2019.
Corresponding Author:
Dr. Moumita Hazra,
D/o. Dr. Samaresh Kumar Hazra,
Hazra Nursing Home, P. O. Domjur District,
Howrah- 711405, West Bengal.
E-mail: 17drmoumitahazra80@gmail.com
DOI: 10.18410/jebmh/2019/484

retinoids.[13,14,15,16,17] Topical retinoids are a first-line treatment for acne vulgaris.[18,19] Nadifloxacin, a newer topical fluoroquinolone, is bactericidal, anti-inflammatory and mildly comedolytic.[10] Nadifloxacin inhibits the enzyme DNA gyrase that is involved in bacterial DNA synthesis and replication, thus inhibiting the bacterial multiplication.[20] Topical adapalene and topical tretinoin might rarely produce adverse effects, such as, erythema, dryness, scaling, stinging, burning, pruritus of skin and mucous membranes, photosensitivity reactions, muscle and joint pains. Topical nadifloxacin might rarely produce adverse effects, such as, pruritus, burning, irritation, erythema, peeling, flushes, papules, feeling of facial warmth, increased sweating, contact dermatitis, dryness of skin and hot flushes.[9,20,21] Due to less data available, this study was taken up, with an objective to compare the safety of topical 1% nadifloxacin and 0.1% adapalene combination therapy with 1% nadifloxacin and 0.025% tretinoin combination therapy, in mild to moderate acne, in tertiary care hospitals, in India.

METHODS

This multi-centre, prospective, open-labelled, randomized, comparative, rational pharmacotherapeutic study was conducted among patients, suffering from mild to moderate acne on their faces, attending the out-patient departments of Dermatology and the study literature was compiled in the departments of Pharmacology and Dermatology of K. D. Medical College, Hospital and Research Centre, Delhi-Mathura Road, Mathura, Uttar Pradesh, India and J. J. M. Medical College, Bapuji Hospital and Chigateri General Hospital, Davangere, Karnataka, India.

The study period was 5 months- The research study was conducted from December 2013 to March 2014, and the study literature was compiled from December 2015 to February 2016.

The inclusion criteria were: (a) patients aged 12-25 years of either sex, (b) patients with mild to moderate acne (grade - I & II) on face above the jaw line, (c) women of child bearing potential are required to have a negative urine pregnancy test result and to agree to use an effective form of contraception for the duration of study (12 weeks), (d) patients who have given consent and are willing to go for a follow-up.

The exclusion criteria were: (a) patients with severe acne vulgaris (grade - III & IV), (b) patients with acne lesions, predominantly involving trunk (truncal acne), (c) other variants of acne: chloracne, oil acne, tropical acne, mechanical acne, severe variants like acne conglobata and acne fulminans, (d) drug induced acne, (e) if at follow-up, disease progresses and necessitates systemic therapy, (f) patients not willing to give informed consent and follow-up, (g) pregnancy and lactating mother, (h) patients with known hypersensitivity to any of the components of the drug, (i) female patients using hormonal contraceptives, (j) patients who are already on topical therapy for acne or any other topical therapy, during the previous four weeks, (k) immunocompromised and patients on medication for any chronic medical illness.

The sample size was 100. The patients were registered, and they received the treatment regimens under the direction of a treating dermatologist. The patients underwent an antibiotic culture and sensitivity test and pre-medication dermatological topical retinoid application patch test, before the further administration of the more suitable and safer antibiotic and retinoid combination therapy, among the two regimens under study. A detailed history was obtained with the proforma, giving special attention to the predisposition to acne. At first visit, the patients were interviewed for their detailed demographic profile, present and past history, obstetric and gynaecological history for female patients, family history, personal history and medication history. Complete general physical examination and systemic examination, including obstetric and gynaecological examination, were performed. Then, thorough dermatological evaluations were made.

The 100 patients, suffering from mild to moderate acne on their faces, were randomly allocated into group A and group B of 50 patients each, for administering the prescribed treatment regimen allotted. Then, keeping in consideration, the results of the antibiotic culture and sensitivity test and the pre-medication dermatological topical retinoid application patch test, group A (50 patients) were instructed to apply topical 1% nadifloxacin and 0.1% adapalene combination therapy and the group B (50 patients) were instructed to apply topical 1% nadifloxacin and 0.025% tretinoin combination therapy. Before the application of the topical anti-acne agents, the patients were advised to wash the face with clean water and dry it well. Then the patients were asked to apply 1 fingertip unit (approximately 0.5 gram) of each study medication once daily in the evening, over the affected areas on the face, on the forehead, cheeks, chin and nose, with a thin film evenly spread over the entire face and it was left overnight, under Indian environmental conditions. Special precaution was taken to avoid the periorbital, para nasal and perioral areas. According to the prescription, the patients in group A applied 0.1% adapalene first and the patients in group B applied 0.025% tretinoin first. After half an hour, both group A and group B patients applied 1% nadifloxacin over that, without washing the face.

The required safety assessments were the detailed recorded tolerability assessments (erythema, scaling, dryness, pruritus, burning, stinging) and the reported adverse effects. All clinical medical events, whether observed by the investigator or reported by the subject and whether or not thought to be drug-related, were considered adverse effects and were thoroughly recorded on the appropriate Adverse Event Case Report Form. To determine whether or not a safety and tolerability profile was 'superior', the number of drop-outs due to adverse events and the frequency and relevance and severity of the side effects were taken into consideration.[22] The patients lost to follow-up, and the patients who withdrew from the study voluntarily, were also recorded.

After enrolment in the research study for 3 months, on 0, 15, 30, 60, 90 days, and on subsequent follow-up visits, after the research study was completed, the occurrence of

any adverse effect, like erythema, scaling, dryness, pruritus, burning, or stinging, was assessed by the Local Irritation Scale, among both the groups of patients. Safety assessments were conducted for all the subjects at each visit, by the scale, depicted in Table 1.[19,23] Safety Assessment was graded at the baseline visit, each post-baseline visit and further follow-up visits.[21]

The data was statistically analysed, with the calculation of Z values and p values, along with the Z test for proportions.

Erythema- Abnormal Redness of the Skin		
Grade	**Score**	**Description**
None	0	No evidence of erythema present
Mild	1	Slight pink discoloration
Moderate	2	Definite redness
Severe	3	Marked erythema, bright red to dusky red in color
Scaling- Abnormal shedding of the stratum corneum.		
Grade	**Score**	**Description**
None	0	No scaling
Mild	1	Barely perceptible, fine scales present to limited areas of the face
Moderate	2	Fine scale generalized to all areas of the face
Severe	3	Scaling and peeling of skin over all areas of the face
Dryness- Brittle and/or tight sensation		
Grade	**Score**	**Description**
None	0	No dryness
Mild	1	Slight but definite roughness
Moderate	2	Moderate roughness
Severe	3	Marked roughness
Pruritus- Scratching sensation of the skin		
Grade	**Score**	**Description**
None	0	No itching
Mild	1	Slight itching, not really bothersome
Moderate	2	Definite itching that is somewhat bothersome
Severe	3	Intense itching that may interrupt daily activities and / or sleep
Burning-Scorching pain sensation immediately after (within 5 minutes) dosing		
Grade	**Score**	**Description**
None	0	No burning
Mild	1	Slight burning sensation, not really bothersome
Moderate	2	Definite warm, burning sensation that is somewhat bothersome
Severe	3	Hot burning sensation that causes definite discomfort and may interrupt daily activities and / or sleep
Stinging-Prickling pain sensation immediately after (within 5 minutes) dosing		
Grade	**Score**	**Description**
None	0	No Stinging
Mild	1	Slight stinging sensation, not really bothersome
Moderate	2	Definite stinging sensation that is somewhat bothersome
Severe	3	Stinging sensation that causes definite discomfort and may interrupt daily activities and / or sleep

Table 1. Methods: Scale for Assessment of Safety

RESULTS

A total of 100 Indian patients participated in the study. All the patients completed the study; and there were no drop-outs due to adverse effects, no patients were lost to follow-up, and no patients withdrew themselves voluntarily, throughout the study, as depicted in Figure 1.

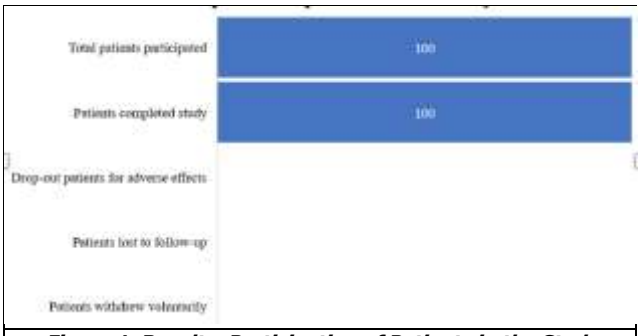

Figure 1. Results: Participation of Patients in the Study

Safety Assessment Period	**3 Months Treatment Duration**					
Adverse Effects	**Group A n (%)**	**If any, Grade, Score**	**Group B n (%)**	**If any, Grade, Score**	**Z value**	**p value**
Erythema	0	None, 0	0	None, 0	0	0, ns
Scaling	0	None, 0	0	None, 0	0	0, ns
Dryness	0	None, 0	0	None, 0	0	0, ns
Pruritus	0	None, 0	0	None, 0	0	0, ns
Burning	0	None, 0	0	None, 0	0	0, ns
Stinging	0	None, 0	0	None, 0	0	0, ns

Table 2a. Adverse Effects of Medications during 3 Months Treatment

Safety Assessment Period	**Follow-Up Period**					
Adverse Effects	**Group A n (%)**	**If any, Grade, Score**	**Group B n (%)**	**If any, Grade, Score**	**Z Value**	**p Value**
Erythema	0	None, 0	0	None, 0	0	0, ns
Scaling	0	None, 0	0	None, 0	0	0, ns
Dryness	0	None, 0	0	None, 0	0	0, ns
Pruritus	0	None, 0	0	None, 0	0	0, ns
Burning	0	None, 0	0	None, 0	0	0, ns
Stinging	0	None, 0	0	None, 0	0	0, ns

Table 2b. Results: Adverse Effects of the Medications, During the Follow-Up Period

In both the groups of patients, group A and group B, receiving topical nadifloxacin and adapalene combination therapy, and topical nadifloxacin and tretinoin combination therapy, respectively, no occurrence of any adverse effect, like, erythema, scaling, dryness, pruritus, burning or stinging, was observed due to the study medications; and there was no statistically significant difference among the observations, during safety assessment for 3 months treatment duration, as depicted in Table 2a, and during the follow-up period, as depicted in Table 2b.

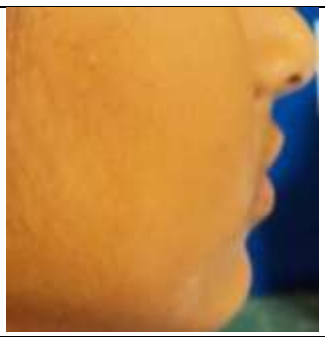

Figure 2. Results: Patient's Face, after Topical Anti-Acne Treatment, with No Adverse Effects

Figure 2 shows the reduced lesion counts on the face of the patient in the study, with no occurrence of adverse effects, after topical anti-acne treatment.

DISCUSSION

Acne vulgaris is a common skin disease characterized by non-inflammatory follicular papules or comedones and by inflammatory papules, pustules and nodules in its more severe forms. The pathogenesis of acne vulgaris is multifactorial. Four main key factors responsible for the development of acne lesions are follicular epidermal hyperproliferation with subsequent plugging of the follicle, excess sebum production, the presence and activity of Propionibacterium acnes and inflammation.[1,2,3,4]

Topical combination anti-acne therapy is patient compliant and cost-effective, as it has synergistic and additive actions on multi-pathogenetic factors, enhancing therapeutic efficacy as greater comedolytic, better anti-inflammatory with more reduction in lesion counts, while minimising adverse effects.[5,6,7,8] Topical retinoids are safe and efficacious for the treatment of acne vulgaris.[18] Topical retinoids target the microcomedones, which are the precursor of acne lesions, and are also the preferred drugs for maintenance therapy.[24]

Adapalene, is more stable chemically, less photo-labile, and more lipophilic, which enables it to penetrate follicles quickly. Fluorescence microscopic studies have shown that adapalene microcrystals penetrate follicular openings to the level of sebaceous gland within 5 minutes of application.[15] The selective uptake by follicles is thought to be due to its lipophilicity and may contribute to adapalene's success in the treatment of acne. Adapalene loaded tristearin, soya lecithin based solid lipid nanoparticles (SLNs-A) has salient features like controlled release, target ability, potential of penetration, improved physical stability, low cost compared to phospholipids, and ease of scaling-up that make solid lipid nanoparticles (SLNs) better than liposomes for effective drug delivery of adapalene.[16] As it also has anti-inflammatory action and only a trace of drug is absorbed systemically, it is preferred.

Topical retinoids, like adapalene or tretinoin, through a thinning effect on stratum corneum, facilitate percutaneous penetration of topical antibiotics, and help to achieve higher concentrations of the antimicrobial agent in the pilosebaceous canal which Propionibacterium acnes inhabits. Anti-acne monotherapy with 1% nadifloxacin does not produce bacterial resistance, if applied for a short span anti-microbial regimen of a period of 3 months, at a topical minimal dose of 1 fingertip unit (approximately 0.5 gram) once daily in the evening, over the affected areas on the face, under Indian environmental conditions. The combination therapy of 1% nadifloxacin with 0.1% adapalene or 0.025% tretinoin is also helpful and is recommended, because it prevents or reduces bacterial resistance.[17] Also, 1% nadifloxacin does not produce any cross-resistance with any other antibiotic or with another fluoroquinolone.[25]

Topical tretinoin has been approved for use in dermatology for 40 years and is currently approved for the treatment of acne vulgaris and photodamage. During this time, topical tretinoin has accumulated significant efficacy and safety data in the treatment of acne and photodamaged skin and demonstrated clinical potential for treating a range of other dermatologic conditions.[26] Tretinoin stabilizes lysosomes, increases ribonucleic acid polymerase activity, increases prostaglandin E2, cAMP and cGMP levels, and increases the incorporation of thymidine into DNA. It acts in acne by its decreased cohesion between epidermal cells and increased epidermal cell turnover, resulting in the expulsion of open comedones into open ones.[21] It fades post-acne pigmented spots and leathery post-acne skin surface.[12] In the epidermis, retinoids induce epidermal hyperplasia in atrophic skin and reduce keratinocyte atypia. Topical tretinoin is relatively photo-labile and thus should be applied once every night. Retinoids are used in the treatment of acne vulgaris, photoaging, particularly mottled hyperpigmentation and fine wrinkles, actinic keratoses, solar lentigines (comprehensive anti-photodamage therapy); and they have significant roles in vision, regulation of cell proliferation and differentiation and bone growth, immune defense and tumour suppression.[9,21,27]

The objective of this rational pharmacotherapeutic study was to do a comparative assessment of the safety of topical 1% nadifloxacin and 0.1% adapalene combination therapy with topical 1% nadifloxacin and 0.025% tretinoin combination therapy, in mild to moderate acne, in tertiary care hospitals, in India. A total of 100 Indian patients participated in the study. All the patients completed the study; and there were no drop-outs due to adverse effects, no patients were lost to follow-up, and no patients withdrew voluntarily, throughout the study. In this study, in both the groups of patients receiving topical nadifloxacin and adapalene and topical nadifloxacin and tretinoin, no adverse effects were observed in the study; and there was no statistically significant difference among the observations. These study observations corroborate the study observations in similar previous studies of safety assessment of topical anti-acne monotherapies or combination therapies.[3,5,6,7,8,11,12,23,24,25,26,28]

Being RAR-selective retinoids, adapalene and tretinoin are more associated with occasional mucocutaneous and musculoskeletal adverse effects, mild in nature, unlike retinoid X receptors (RXR)-selective retinoids, which induce physiochemical adverse effects, moderate to severe in

nature. Topical application of retinoids are rarely associated with mild adverse effects, unlike systemic retinoids which are comparatively more associated with moderate to severe adverse effects. Adapalene and tretinoin, improves dyspigmentation through anti-AP-1 (activator protein) mechanism, which is a transcription factor composed of c-Jun and c-Fos, regulate the expression of vascular endothelial growth factors and activate the synthesis of metalloproteinases on UV irradiation. They thin the stratum corneum by decreasing the number of cell layers, which leads to mild photosensitivity. Adapalene does not bind to cytosolic receptor protein, hence it has no affinity for cellular (cytosolic) retinol binding protein, and does not induce cytosolic retinol binding protein II messenger ribonucleic acid and thus it is very rarely associated with skin irritation, but it induces CRBP II messenger ribonucleic acid when applied under occlusion for 4 days to human skin; unlike tretinoin, which has higher and undisputed topical anti-acne therapeutic efficacy, but due to its capacity to bind cytosolic retinoid-activating binding proteins, is associated with mild skin irritation, occasionally. Available formulations with co-polymer microspheres, prepolyolprepolymer-2, hydrogels or micronized tretinoin, for slow release of tretinoin, and concomitant use of emollients, or combination therapy decrease skin irritation.[9,14,21,29,30,31,32] Topical nadifloxacin very rarely causes mild cutaneous adverse effects.[20,33,34,35]

Studies also suggest that the effectiveness of the highly efficacious and safe topical antibiotic nadifloxacin in inflammatory acne lesions may be attributed to its inhibitory effect on pro-inflammatory cytokines like interleukin (IL)-1α, IL-6 and IL-8, which play an important role in acne pathogenesis. Nadifloxacin also inhibits the enzyme DNA topoisomerase IV, which enhances its anti-bacterial spectrum to Gram-positive, Gram-negative as well as anaerobic bacteria such as Propionibacterium acnes as well as against methicillin-susceptible Staphylococcus aureus (MSSA) and Staphylococcus epidermidis, among others.[20,21,29,36,37,38,39] Therefore, on comparative safety assessment, topical 1% nadifloxacin and 0.1% adapalene combination therapy was found to be as well tolerated and safe as topical 1% nadifloxacin and 0.025% tretinoin combination therapy. This study would be a helpful step for developing newer dermatological anti-microbial, anti-inflammatory and anti-neoplastic diagnostics and therapeutics; for developing faster, more efficacious, safer, more precise and cost-effective therapeutics in patients suffering from acne vulgaris; and for enhancing dermatological health and cure.

CONCLUSIONS

Topical 1% nadifloxacin and 0.1% adapalene combination therapy was as safe as topical 1% nadifloxacin and 0.025% tretinoin combination therapy, in the treatment of mild to moderate acne.

REFERENCES

[1] Zaenglein AL, Graber EM, Thiboutot DM, et al. Disorders of sebaceous glands - acne vulgaris and acneiform eruption. In: Wolff K, Goldsmith LA, Katz SI, et al, eds. Fitzpatrick's Dermatology in Medicine. 7th edn. USA: McGraw-Hill 2008:690-691.

[2] Feldman S, Careccia RE, Barham KL, et al. Diagnosis and treatment of acne. Am Fam Physician 2004;69(9):2123-2130.

[3] Ghoshal L, Banerjee S, Ghosh SK, et al. Comparative evaluation of effectiveness of adapalene and azithromycin, alone or in combination, in acne vulgaris. Indian J Dermatol 2007;52(4):179-183.

[4] Simpson NB, Cunliffe WJ. Disorders of sebaceous glands. In: Burns T, Breathnach S, Griffiths C, et al, eds. Rooks textbook of dermatology. 8th edn. USA: Blackwell: Massachusetts 2010:42.18-43.86.

[5] Gollnick H, Cunliffe W, Berson D, et al. Global alliance to improve outcomes in acne. J Am Acad Dermatol 2003;49(1 Suppl):S1-37.

[6] Feneran AN, Kaufman WS, Dabade TS, et al. Retinoid plus antimicrobial combination treatments for acne. Clin Cosmet Investig Dermatol 2011;4:79-92.

[7] Wolf JE, Kaplan D, Kraus SJ, et al. Efficacy and tolerability of combined topical treatment of acne vulgaris with adapalene and clindamycin: a multicenter, randomized, investigator-blinded study. J Am Acad Dermatol 2003;49(3 Suppl):S211-S217.

[8] Abdel-Naser MB, Zouboulis CC. Clindamycin phosphate/tretinoin gel formulation in the treatment of acne vulgaris. Expert Opin Pharmacother 2008;9(16):2931-2937.

[9] Burkhart C, Morrell D, Goldsmith L. Dermatologic pharmacology. In: Laurence LB, Bruce AC, Bjorn CK, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th edn. USA: McGraw Hill 2011:1809-1812.

[10] Roos TC, Jugert FK, Merk HF, et al. Retinoid metabolism in the skin. Pharmacol Rev 1998;50(2):315-333.

[11] Thiboutot DM, Weiss J, Bucko A, et al. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized, double-blind, controlled study. J Am Acad Dermatol 2007;57(5):791-799.

[12] Leyden JJ. A review of the use of combination therapies for the treatment of acne vulgaris. J Am Acad Dermatol 2003;49(3 Suppl):S200-S210.

[13] Schmidt N, Gans EH. Tretinoin: a review of its anti-inflammatory properties in the treatment of acne. J Clin Aesthet Dermatol 2011;4(11):22-29.

[14] Shroot B, Michel S. Pharmacology and chemistry of adapalene. J Am Acad Dermatol 1997;36(6 Pt 2):S96-S103.

[15] Allec J, Chatelus A, Wagner N. Skin distribution and pharmaceutical aspects of adapalene gel. J Am Acad Dermatol 1997;36(6 Pt 2):S119-S125.

[16] Jain AK, Jain A, Garg NK, et al. Adapalene loaded solid lipid nanoparticles gel: an effective approach for acne treatment. Colloid surface B Biointerfaces 2014;121:222-229.

[17] Ioannides D, Rigopoulos D, Katsambas A. Topical adapalene gel 0.1% versus isotretinoin gel 0.05% in the treatment of acne vulgaris: a randomized open-label clinical trial. Br J Dermatol 2002;147(3):523-527.
[18] Kolli SS, Pecone D, Pona A, et al. Topical retinoids in acne vulgaris: a systematic review. Am J Clin Dermatol 2019;20(3):345-365.
[19] Bershad S, Singer GK, Parente JE, et al. Successful treatment of acne vulgaris using a new method: results of a randomized vehicle-controlled trial of short-contact therapy with 0.1% tazarotene gel. Arch Dermatol 2002;138(4):481-489.
[20] Petri WA. Sulfonamides, trimethoprim-sulphamethoxazole, quinolones, and agents for urinary tract infections. In: Laurence LB, Bruce AC, Bjorn CK, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th edn. New York, NY: McGraw-Hill 2011:1463-1476.
[21] Robertson DB, Maibach HI. Dermatologic pharmacology. In: Katzung BG, Masters SB, Trevor AJ, eds. Basic and clinical pharmacology. 12th edn. New York, NY: McGraw-Hill 2012:1069-1071.
[22] Nast A, Dréno B, Bettoli V, et al. European evidence-based (S3) guidelines for the treatment of acne. J Eur Acad Dermatol 2012;26 Suppl 1:1-29.
[23] Leyden J, Wortzman M, Baldwin EK. Tolerability of clindamycin/tretinoin gel vs. tretinoin microsphere gel and adapalene gel. J Drugs Dermatol 2009;8(4):383-388.
[24] Shah BJ, Sumathy TK, Dhurat RS, et al. Efficacy and tolerability of topical fixed combination of nadifloxacin 1% and adapalene 0.1% in the treatment of mild to moderate acne vulgaris in Indian patients: a multicenter, open-labelled, prospective study. Indian J Dermatol 2014;59(4):385-389.
[25] Deshmukh SN, Badar VA, Mahajan MM, et al. Comparison of efficacy and safety of topical 1% nadifloxacin and tretinoin 0.025% combination therapy with 1% clindamycin and tretinoin 0.025% combination therapy in patients of mild-to-moderate acne. Perspect Clin Res 2018;9(4):161-164.
[26] Baldwin HE, Nighland M, Kendall C, et al. 40 years of topical tretinoin use in review. J Drugs Dermatol 2013;12(6):638-642.
[27] Kang S, Goldfarb MT, Weiss JS, et al. Assessment of adapalene gel for the treatment of actinic keratoses and lentigines: a randomized trial. J Am Acad Dermatol 2003;49(1):83-90.
[28] Treesirichod A, Chaithirayanon S, Wongjitrat N. Comparison of the efficacy and safety of 0.1% adapalene gel and 0.025% tretinoin cream in the treatment of childhood acanthosis nigricans. Pediatr Dermatol 2019;36(3):330-334.
[29] Sweetman SC, ed. Martindale's the complete drug reference. 36th ed. UK, USA: Pharmaceutical Press 2009:194-1618.
[30] Thielitz A, Gollnick H. Recent therapeutic developments for acne. Expert Rev Dermatol 2013;8(1):37-50.
[31] Lucky AW, Sugarman J. Comparison of micronized tretinoin gel 0.05% and tretinoin gel microsphere 0.1% in young adolescents with acne: a post hoc analysis of efficacy and tolerability data. Cutis 2011;87(6):305-310.
[32] Kircik LH. Evaluating tretinoin formulations in the treatment of acne. J Drugs Dermatol 2014;13(4):466-470.
[33] De Sarro A, De Sarro G. Adverse reactions to fluoroquinolones, an overview on mechanistic aspects. Curr Med Chem 2001;8(4):371-384.
[34] Iannini PB. The safety profile of moxifloxacin and other fluoroquinolones in special patient populations. Curr Med Res Opin 2007;23(6):1403-1413.
[35] Nelson LS, Lewin NA, Howland MA, et al. Goldfrank's toxicologic emergencies. 9th edn. New York, NY: McGraw-Hill 2011:410-422.
[36] Tunca M, Akar A, Ozmen I, et al. Topical nadifloxacin 1% cream vs. topical erythromycin 4% gel in the treatment of mild to moderate acne. Int J Dermatol 2010;49(12):1440-1444.
[37] Plewig G, Holland KT, Nenoff P. Clinical and bacteriological evaluation of nadifloxacin 1% cream in patients with acne vulgaris: A double-blind, phase III comparison study versus erythromycin 2% cream. Eur J Dermatol 2006;16(1):48-55.
[38] Kurokawa I, Akamatsu H, Nishijima S, et al. Clinical and bacteriologic evaluation of OPC-7251 in patients with acne: A double-blind group comparison study versus cream base. J Am Acad Dermatol 1991;25(4):674-681.
[39] Vogt K, Hahn H, Hermann J, et al. Antimicrobial evaluation of nadifloxacin (OPC-7251), a new topical quinolone, in acne vulgaris. Drugs 1995;49 Suppl 2:266-268.