Effectiveness and Tolerance of Topical Nadifloxacin in the Therapy of Acne Vulgaris (grade I-II): Results of a Non-interventional Trial in 555 Patients

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KEY WORDS: acne vulgaris, nadifloxacin, topical treatment, tolerance, interactions

ABSTRACT

Regulatory approval of topical nadifloxacin for the treatment of acne vulgaris was based on data from controlled and randomised clinical trials using a monotherapy regimen. Frequently in dermatological practice, however, multi-regimen approaches are used. This prospective trial was conducted to assess clinical use and value of topical nadifloxacin in the treatment of acne vulgaris under routine conditions.

A non-interventional trial was performed in 105 dermatological practices in Germany. Inclusion criteria were the presence of acne papulo-pustulosa (acne vulgaris grade I-II)1 and the indication of therapy with nadifloxacin. In addition to treatment characteristics, cardinal disease symptoms and quality of life data were recorded before and after therapy with nadifloxacin. Investigators and patients were asked to rate effectiveness and tolerance of therapy. Data was evaluated in an exploratory sense.

Five hundred fifty five of 589 data sets fulfilled the criteria for evaluation. Mean patient age was 21.3 and patients had a mean history of acne vulgaris of approximately 33 months. 68.5% of the patients received nadifloxacin as monotherapy, 27% had an additional topical treatment, and in 10.3%, systemic medication was also administered. After a mean treatment period of 50.8 days dermal symptoms had significantly diminished. In 81.3% of the whole trial population, the investigators rated the effectiveness as “very good/good”. A slightly better appraisal was obtained for nadifloxacin monotherapy (82.1%) while efficacy assessment for the combination of nadifloxacin and additional topical therapy was slightly inferior (77.5%). The patient rating for the concomitant administration of systemic medication was comparable to nadifloxacin monotherapy (82.4%).

The reduction of dermal symptoms was

accompanied with a clear improvement in the patients' psychic disposition and quality of life.

Tolerance of nadifloxacin was rated "very good/good" by 98% of the investigators and by 96.6% of the patients.

Topical monotherapy of acne vulgaris grade I-II with nadifloxacin is as effective and safe under practice conditions as earlier demonstrated in controlled clinical trials. Supplementary topical treatment with other anti-acne products did not reveal impaired tolerance of nadifloxacin.

INTRODUCTION

Acne vulgaris is a common skin disease usually starting around puberty. The disease mostly affects the face, the back and the chest, and is characterised by non-inflammatory open and closed comedones, and by inflammatory papules and pustules. The mainstays in the therapy of mild to moderate forms of acne vulgaris are topical keratolytics (e.g. benzoyl peroxide, retinoids, azelaic acid) and topical antibiotics (e.g. tetracycline, erythromycin).[2] In the year 2000*, the fluoroquinolone antibiotic nadifloxacin obtained marketing authorisation in the EU for the topical treatment of acne vulgaris grade I-II. Nadifloxacin is highly active against aerobic and anaerobic bacteria isolated from patients with infected skin diseases.[3, 4] Investigations of the clinical efficacy of nadifloxacin 1% cream in the treatment of acne vulgaris demonstrated equal clinical results compared to erythromycin 2%.[5, 6]

The present trial is focused on the investigation of the clinical use, and the efficacy and safety of nadifloxacin in the treatment of acne vulgaris grade I-II under routine conditions.

MATERIALS AND METHODS

589 patients were entered into this non-interventional trial performed in 105 dermatological practices in Germany. Inclusion criteria were the presence of acne vulgaris grade I-II[1] and the indication for a therapy with nadifloxacin cream 1% (Nadixa® cream). With regard to dosing and treatment period, investigators were advised to abide by the instructions in the package leaflet.

The individual case report forms required the following data to be collected during the first patient visit: demography, history, localisation and severity of acne vulgaris, medical and cosmetic acne

Table 1: *Psychological situation before / after treatment*

		Presence of symptom									
Symptom		very severe		severe		moderate		not present		no data	
		%	(n)	%	(n)	%	n	%	n	%	n
Shame	before	10.5	(58)	41.8	(232)	37.1	(206)	10.1	(59)	--	(--)
	after	1.8	(10)	15.1	(84)	53.5	(297)	29.2	(162)	0.4	(2)
Frustrating/aggressive events	before	3.1	(17)	17.2	(73)	44.4	(247)	20.2	(112)	--	(--)
	after	0.4	(2)	3.6	(20)	35.3	(196)	60.5	(336)	0.2	(1)
Impairment of social contacts	before	2.9	(16)	13.9	(77)	42.1	(234)	41.1	(228)	--	(--)
	after	0.4	(2)	3.9	(22)	33.7	(187)	61.8	(343)	0.2	(1)
Averseness to being seen in public	before	5.4	(30)	33.1	(184)	37.1	(206)	24.1	(134)	0.2	(1)
	after	1.0	(6)	7.7	(43)	44.5	(247)	46.5	(258)	0.2	(1)
Impaired sense of self-esteem	before	6.8	(38)	35.5	(197)	38.4	(213	18.9	(105)	0.4	(2)
	after	0.9	(5)	10.1	(56)	45.9	(255)	42.7	(237)	0.4	(2)

Degree of psychological impairment after therapy with nadifloxacin (n=555). Pre-treatment data are given for comparison.

Table 2: *Severity of acne vulgaris symptoms before and after treatment*

Symptom		Patients					
		%	n	%	n	%	n
		< 20		> 20		no data	
Comedones	before	44.5	(247)	53.9	(299)	1.6	(9)
	after	75.1	(417)	22.7	(126)	2.2	(12)
		< 10		10-20		no data	
Pustules	before	34.5	(219)	60.0	(333)	0.5	(3)
	after	87.9	(488)	9.4	(52)	2.7	(15)
		none		< 10		no data	
Nodules (<1 cm)	before	44.1	(228)	54.8	(304)	4.1	(23)
	after	70.1	(389)	24.5	(136)	5.4	(30)
		none		pronounced		no data	
Inflammation	before	17.1	(95)	80.4	(446)	2.5	(14)
	after	72.8	(404)	18.9	(105)	6.5	(36)

Severity of acne vulgaris symptoms before and after therapy with nadifloxacin cream in 555 patients.

pre-treatment, and the patient's psychic disposition (self assessment). On visit 2, the following was to be recorded: administration details for nadifloxacin, treatment period, concomitant medical and cosmetic acne treatment, severity of acne, investigator's and patient's assessment of effectiveness and tolerance, the patient's psychic disposition (self assessment), and any adverse drug effects.

Data was entered into the computer and analysed by SPSS 10 statistical software.

In compliance with German drug law, competent authorities were given notice of the study and the official recommendations for the conduct of non-interventional trials were observed [7].

RESULTS

Trial population and basic demographic data

Of the 589 case documentations obtained, data from 34 patients was excluded from analysis due to violations of the trial protocol (retrospective or very scanty documentation), rendering 555 valid data sets for evaluation.

38.2% of the patients were male and 59.6% female (no data in 2.2%). The mean age of the patients was 21.3 ±7.9 years (median 19, min. 11, max. 68).

History, localisation and severity of acne vulgaris at baseline

At visit 1, patients had a mean acne vulgaris history of 32.7 ± 38.5 months (median 24, min 0.5, max 420). Affected body parts were the face (96.8%), the back (27.2%), the chest (18.9%), and the neck (11.0%). Table 1 gives an overview of the presence and severity of dermal symptoms at study entry. The presence of nodules and significant inflammatory affections suggests that the trial population was not limited to patients with acne vulgaris grade I-II but also included more severe forms.

Anti-acne therapy before study entry and psychological strain

At study entry, 59.8% of the patients had already received topical pre-treatment; a systemic pre-treatment was documented in 19.5% of the trial population.

The most frequently prescribed topicals were erythromycin (35.9%), benzoyl peroxide (29.9%) and tretinoin/isotretinoin (20.4%), whereas minocyclin (56.5%) and doxycyclin (20.3%) were the most commonly used systemic drugs. Tolerance of topical pre-treatment was predominantly judged as "very good or good" in the case of erythromycin, but moderate, poor or very poor when benzoyl peroxide and tretinoin/isotretinoin had been used (Fig. 1). More

Table 3: *Rating of treatment efficacy*

	Investigator		Patient	
	%	(n)	%	(n)
Very good	35.5	(197)	32.8	(182)
Good	45.8	(254)	44.1	(245)
Moderate	15.5	(86)	16.8	(93)
Poor	3.0	(17)	5.0	(28)
Very poor	--	(--)	1.1	(6)
No data	0.2	(1)	0.2	(1)
Total	100	(555)	100	(555)

Rating of treatment efficacy by investigators (n=105) and patients (n=555)

than 29% of the patients had also received cosmetic acne treatment.

The degree of psychic impact caused by the presence of acne symptoms which the patients experienced at study entry are summarised in Table 1: More than 50% of the patients had a very strong/strong feeling of shame and more than 40% indicated a strongly/very strongly impaired sense of self-esteem.

Therapy regimens in this trial

Eighty percent of the patients were instructed to apply nadifloxacin twice daily, 20% only once a day thus falling short of the official application instruction. The mean treatment period was 50.8 ± 15.9 days (median 50, min. 7, max. 137). 66.1% of the patients stated having applied the cream very regularly, 30.6% said that they had skipped the application once in a while.

Topical anti-acne treatment with other medicinal products supplementary to nadifloxacin cream was documented in 150 patients (27.0%) and 57 patients (10.3%) received concomitant systemic treatment, whereas 68.5% of the patients were treated with nadifloxacin alone. The most frequent additionally prescribed topicals were benzoyl peroxide (44.0%), adapalene (22.0), and tretinoin/isotretinoin (16%), whereas minocyclin (47.4%) and doxycyclin (19.3%) were the most commonly used systemic drugs. 26.8% of the patients also received cosmetic acne treatment.

Severity of acne symptoms after treatment

After the therapy with nadifloxacin cream a clear reduction of all dermal symptoms was evident (Table 2). For instance, the fraction of patients without any signs of inflammation had more than quadrupled and the proportion of patients with > 20 comedones was reduced from 53.9% to 22.7%. Moreover, a marked decrease in patients with more than 10 putrid pustules was observed after topical treatment with nadifloxacin (Fig. 2).

Acne related psychological strain after treatment

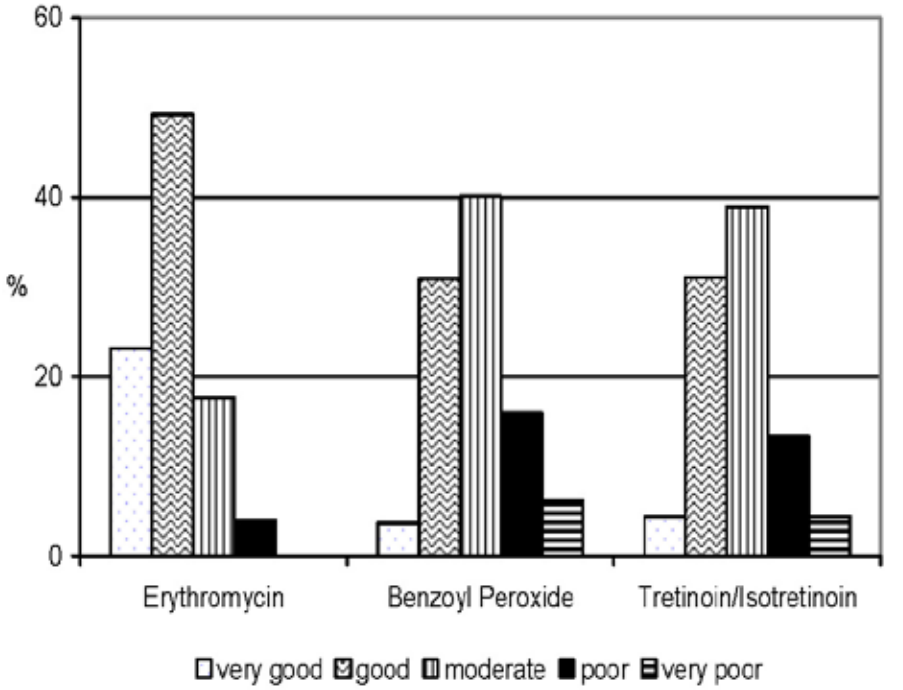
Table 1 summarises the changes in the patients' psychological disposition after treatment: The proportion of patients feeling very strong/strong shame had dropped from more than 50% to 16.9%, while the fraction of patients with a strongly impaired sense of self-esteem was reduced from over 40% to 11.0%.

Investigators' and patients' rating of treatment efficacy

The general assessment of treatment efficacy by investigators and patients is given in Table 3. In 81.3% of the cases the investigators rated the therapy outcome as "very good or good" and only in 3.0% as "poor". The patients' ratings were widely comparable.

Figure 3 shows the differentiated evaluation of the investigators' efficacy rating depending on the chosen treatment regimen. In 82.1% of cases, the efficacy of monotherapy with nadifloxacin was rated as "very good or good". Efficacy of topical anti-acne treatment supplementary to nadifloxacin was slightly less positively rated (77.5 % of the cases), and efficacy of concomitant systemic anti-acne treatment was judged as "very

***Figure 1**. Tolerance rating of different topical anti-acne products administered before inclusion in the study (in percent of patients pre-treated).*



Patients' tolerance-evaluation of different anti-acne products administered before inclusion in the study.

good or good" in 82.4%.

A clear correlation was seen between the treatment duration and the proportion of the efficacy rating "very good or good". The respective proportion rose from 65.0% after 4 weeks to 77.6% after 6 weeks and further increased to 81.4% after 8 weeks.

Treatment tolerance

General tolerance of topical nadifloxacin treatment was rated as "very good or good" by 98.0% of the investigators and 96.6% of the patients. 2.1% of the patients judged the treatment tolerance as "moderate", and a further 1.1% as "poor or very poor".

Tolerance of combined topical anti-acne treatment with nadifloxacin (n = 150) was predominantly judged as "very good or good" for tretinoin/isotretinoin (74.9%), adapalene (90.9%), azelaic acid (78.6%) and benzoyl peroxide (85.6%). A total of 15 patients reported moderate tolerance when tretinoin/isotretinoin, adapalene or bezoyl peroxide were administered supplementary to nadifloxacin cream. Combined treatment with azelaic acid was evaluated as "poor" in 2 patients (Fig. 4).

Therapy withdrawals and side effects

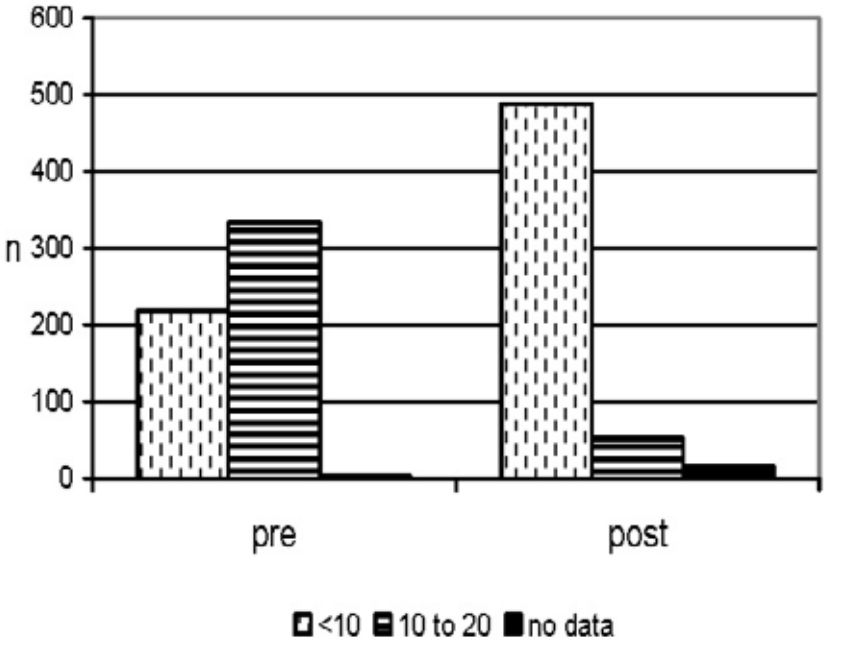
Treatment with nadifloxacin was prematurely terminated in 8 cases (1.4%), 7 of which were due to lack of efficacy and/or lacking acceptance by the patient and in 1 case due to a newly diagnosed pregnancy.

Two patients (0.4%) reported side effects. In one patient under concomitant medication with topical azelaic acid, an increase of dermal efflorescences attributed to nadifloxacin was observed. In the other case, the patient reported erythema and the investigator assumed a causal relationship with supplementary administered adapalene.

DISCUSSION

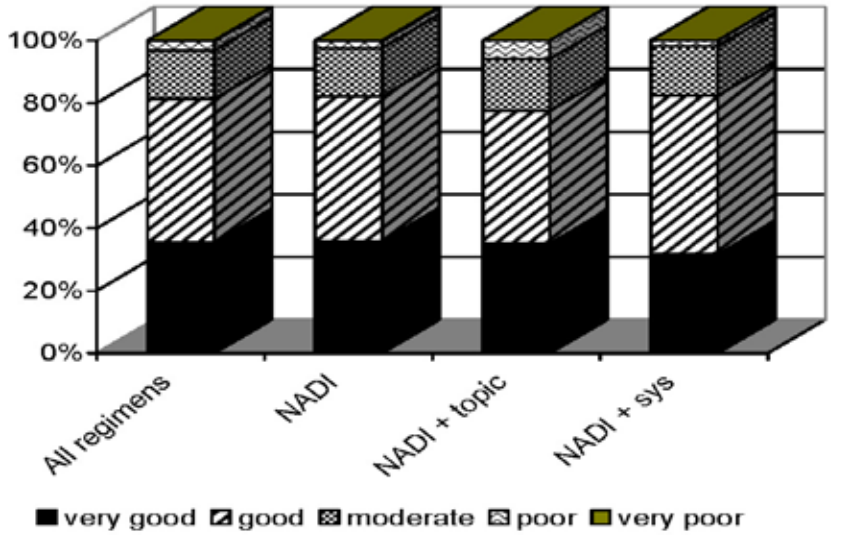
.It is generally accepted that antibiotics play a key role in the therapy of acne vulgaris. While systemic antibiotics are especially valuable in the therapy of moderate to severe cases, topical antibiotics are very effective in mild to moderate stages of acne vulgaris.8.

***Figure 2**. Changes in inflammatory acne pustules in 555 patients treated with nadifloxacin*



Changes in putrid pustules in patients treated with nadifloxacin

***Figure 3.** Investigators efficacy rating of different nadifloxacin treatment regimens (in %)*



Investigators' efficacy rating of different nadifloxacin treatment regimens; percentages of ratings are given (NADI= Nadifloxacin monotherpy, NADI + topic= Nadifloxacin plus additional topical treatment, NADI + sys= Nadifloxacin plus systemic anti-acne treatment).

The topical antibiotic nadifloxacin, investigated in this non-interventional trial, was shown to be very effective as a monotherapy as confirmed by 82.1% of "very good/ good" efficacy ratings. Dermal symptoms as well as the psychological disposition of the patients improved considerably over the treatment period.

Combined administration of nadifloxacin with other topical anti-acne preparations, occuring in 150 patients, did not lead to an impaired local tolerance. This observation is in accordance with those of Wigger-Alberti et al. 20089 who did not find a cumulative irritation potential of nadifloxacin cream when administered combined with other topical anti-acne products.

However, supplementary systemic therapy with other anti-acne compounds did not yield a verifiably better appraisal of therapy success by investigators or patients. Contrary to general recommendations for the concomitant use of topical antibiotics and other compounds,10 the results of this trial did not show advantage of the combined administration of another topical preparation in addition to nadifloxacin. In these cases, slightly less favourable efficacy results were achieved as when compared to nadifloxacin alone.

Compared to other antibiotics used in the systemic and topical therapy of acne vulgaris, such as erythromycin or clindamycin for which considerable development of bacterial resistance by Propionibacterium acnes has been reported.[9, 12, 13, 14, 16, 17] No changes in the susceptibility of relevant bacteria have been observed for the chinolone nadifloxacin[3, 4, 12, 14, 15] even after two years of topical use in Germany.[13]

CONCLUSION

Nadifloxacin cream is an effective and safe monotherapy for mild to moderate forms of acne vulgaris. Supplementary application of systemic or topical compounds was well tolerated.

COMPETING INTERESTS

The study was funded by Dr. Pfleger GmbH, the German distributor of nadifloxacin.

Helmut Schöfer is a full-time employee and senior physician of the University Clinic of Dermatology and Venerology in Frankfurt/M. He was involved in several clinical trials and expert reports as advisor and investigator for the Dr. R. Pfleger GmbH. Ulrich Schwantes is a full-time employee of Dr. Pfleger GmbH. Werner Kusche is a full-time employee of A.CRO Clinical Research Services GmbH, contracted by Dr. Pfleger GmbH to evaluate and report the trial data.

AUTHORS' CONTRIBUTIONS

US and HS conceived the study, and participated in their design. AG managed all administrative and organizational concerns during the study including data verification. WK was responsible for trial data evaluation and reporting and drafting the manuscript. US, and HS take responsibility for the interpretation of the results and for critical revision of the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors wish to thank all contributing dermatologists in Germany for their valuable cooperation. We thank Anna Wolf (Dr. R. Pfleger GmbH) for proof-reading the manuscript.

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