Original paper

The use of isotretinoin in acne therapy in early childhood and its effect on the occurrence of acne symptoms later in life. Eight-year follow-up

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Abstract

Introduction: Acne vulgaris is a chronic inflammatory skin disease of the pilosebaceous follicles that affects patients of all ages.
Aim: Use of isotretinoin in the early stages of the disease to prevent subsequent lesions of acne, including prolonged treatment and acne scars at a later age.
Material and methods: A retrospective, comparative study was carried between January 2010 and November 2018. The study population consisted of 90 children aged 9–18 years with acne. During treatment by isotretinoin the clinical evaluation was done every month. Patients were divided into three groups according to age. One of the qualification criteria was follow-up visits.
Results: A total of 90 children (67.8% females; mean age: 13.5 years) were enrolled. In group A (30 individuals – aged 9–11) and B (30 individuals – aged 12–13), treatment was terminated 2 months after clinical improvement (mean: 3 months). In control group C (30 individuals – aged 14–18), treatment was carried out using average cumulative dose 135 mg/kg bw/day. All groups showed up for follow-up. after 1 to 8 years. In groups A and B, 13 people underwent a second acne treatment; in 3.33% oral isotretinoin was used, in 18.33% topical treatment. In group C, 30 (100%) individuals underwent a second acne treatment; in 20% oral isotretinoin was used, and 80% required a topical treatment. Acne scars and post acne hyperpigmentation have been documented in 73.33% in group C.
Conclusions: Early, reasonable and short-term use of isotretinoin can reduce the incidence of acne in the future and reduce the occurrence of secondary acne symptoms.

Key words: acne, acne treatment, early childhood, isotretinoin, paediatric acne.

Introduction

Acne vulgaris is a chronic inflammatory dermatosis of the pilosebaceous follicles, with comedones as a hallmark of the disease. Acne vulgaris occurs in seborrheic areas with a characteristic peak of prevalence during adolescence. It is believed that acne affects up to even 100% of young people, when taking into account its mild forms [1]. Acne vulgaris is one of the most common skin conditions in children and adolescents, and 12 years of age is no longer considered the lower end of the age range for acne onset [2, 3]. Currently, acne does not only affect children during adolescence [4]. The epidemiology of this dermatosis is evolving, and the symptoms of acne occur from birth to the age of 8 and later on until the end of adolescence. Now, childhood acne is not linked to endocrinological diseases in most of the cases. And it is considered a normal variant of acne. Davis *et al.* in their study described 55 million paediatric acne visits [5]. Where neonatal and infantile acne was 3% of visits overall, mid-childhood acne accounted for 0.9% of cases and pre-adolescent acne accounted for 4.8% of total childhood acne. In research by Napolitano *et al.* (683 children), acne was present in 34.3% of the patients, and its preva-

lence increased with age being higher after 13 years of age (36.3%) and lowest at 9 years of age (6%) [6]. The pathogenesis of acne vulgaris is multifactorial. The four major identified factors are: excess sebum production, follicular epidermal hyperkeratinisation, the proinflammatory effects of *Cutibacterium acnes* and other normal skin flora, and inflammation [7]. However inflammation is the most important cause of aetiology of acne. There are multiple factors involved in acne: hyperkeratosis of the follicular duct, sebum hypersecretion by androgenic stimuli, and secretory duct colonization with the *Cutibacterium acnes* resulting in ongoing inflammation. The primary cause is unknown. There are some aggravating factors of acne [7, 8]: increased androgen hormone levels; comedogenic cosmetics and skin care products; mechanical factors such as excessive friction, rubbing, stretching, compression; sun exposure and UV light. Medical drugs like corticosteroids, bromide, chloride, halothane, iodide, oral contraceptives, isoniazid, ACTH, thyroid hormone, progesterone, phenytoin, coal tar, or lithium or chemicals like chlorinated hydrocarbons and petrol are connected with acneiform eruptions. It also highlights the role of cytokines in the pathogenesis of acne [1]; the TLR2 receptors which are stimulation by P. acnes and increases interleukin 8 and 12 levels. Recently, acne has been suggested as a visible indicator of systemically exaggerated mammalian target of rapamycin complex 1 (mTORC1) signalling. mTORC1 is a protein complex which plays a crucial role in protein and lipid synthesis, cell growth and proliferation [9]. Isotretinoin is a vitamin A analogue, which is readily isomerized to tretinoin. It causes normalization of abnormal keratinisation. It also reduces sebum secretion. Furthermore, it has anti-inflammatory as well as antibacterial properties. Oral isotretinoin targets all of the pathophysiologic factors involved in acne typically producing excellent results [2, 10]. Many studies suggest early therapy in childhood acne, but this is purely informational and screening.

Aim

In our study, oral isotretinoin was used in children (9–18 years) requiring anti-acne treatment by isotretinoin to prevent subsequent lesions of acne, including prolonged treatment and acne scars at a later age. In an 8-year follow-up, acne evolution was observed.

Material and methods

This retrospective, comparative study was carried in Poland from January 2010 to November 2018 in children aged 9–18 years with mild to severe acne vulgaris. 90 patients were included in this study with a follow-up of 8 years after oral treatment with isotretinoin from March 2010 to November 2018.

The comparative method was used as a point of reference for the need to initiate early acne treatment and the possible consequences of not taking such measures, which would have an impact on the subsequent occurrence of acne lesions, severely affected by acne, and the associated costs.

Inclusion criteria: age above 9 years and of both sexes; participants having mild, moderate to severe facial acne vulgaris; participants willing to undergo treatment and follow-up; parental agreement to start treatment with oral isotretinoin.

Exclusion criteria: age above 18 years; patients who intend to consume alcohol during the treatment course; presence of any renal or hepatic compromise or any pre-existing hyperlipidaemia; coexistence of any other dermatoses involving the face; immunocompromised patients; patients with medical diseases like diabetes mellitus or epilepsy; patients unwilling to undergo the necessary investigations; patients unwilling (or not able) to attend later post-treatment follow-up visits.

Full history was taken from each patient including: age, gender, duration of disease and previous treatment. Physical examination was done to evaluate the severity of acne. Scoring of severity of acne was carried out using the Global Acne Grading System (GAGS) [11]. The system considers six locations on the face and chest/upper back, with a factor for each location based strictly on the surface area (forehead = 2, right cheek = 2, left cheek = 2, nose = 1, chin = 1, chest and upper back = 3), distribution, and density of pilosebaceous units. Acne was defined as mild acne in which the count of pustules is less than 20 and the count of papules is less than 10, moderate acne in which the count of pustules is ranging between 20 and 40 and the count of papules is ranging between 10 and 30 and severe acne in which the count of pustules is more than 40 and the count of papules is more than 30. Exclusion criteria were: single papules or comedones, and coexistence of any other dermatoses involving the face and allergy to medications, immunocompromised patients, diseases or drugs that interfere with clotting systems, patients with medical diseases like diabetes mellitus or epilepsy. Formal consent was taken from all parents of the patient before starting the trial of treatment, after full explanation of the nature of the disease, course, treatment, prognosis and its complications, the target of the present work regarding the drug, its efficacy, side effects, the method and duration of treatment and follow-up. Patients were instructed to use retinoid as a single dose in the morning. The clinical evaluation was done every month. Side effects were recorded at each visit. All patients had laboratory tests performed (peripheral blood morphology with smear, triglycerides, total cholesterol, low-density lipoprotein (LDL), amylase, bilirubin, asparagine amino transferase (AST), alanine amino transferase (ALT), γ-glutamyl transpeptidase (GGTP), glucose, alkaline phosphatase). Patients were divided into

three groups according to age, Group A: 30 individuals – aged 9–11, Group B: 30 individuals – aged 12–13, and control Group C; 30 individuals – aged 14–18. Group C is a control group, including patients with acne, who have not previously been treated for isotretinoin. These are patients with moderate, severe and inflammatory acne vulgaris; with symptoms of acne from the beginning of adolescence. The study was conducted from January 2010 to November 2018; and observation after treatment was carried out from March 2010 to November 2018.

Statistical analysis

Statistical analysis was done using SPSS version 20 (Statistical Package for Social Sciences).

Comparison between groups was done by using independent sample t-test. Comparison before and after treatment (in each group) was done by paired t-test, comparison of the reduction rate of the lesions in both groups was done by using χ^2 test. A p-value < 0.05 was considered as significant.

Demographic data and adverse side effects after taking isotretinoin (10, 20 or 30 mg) did not differ considerably between the three presented groups and were not statistically notable (Table 1).

Results

The study population of 90 participants included 29 (32.2%) males and 61 (67.8%) females. The age range was 9–18 years with a mean ± SD of 13.5 ±3.02 years. All patients were treated with oral isotretinoin (dose of titrated according to the severity of lesions). The dose was adjusted based on the weight of the body. The average weight was 23.50 ±16.26 kg. Oral isotretinoin was dosed as 10, 20 or 30 mg/day for an isotretinoin dose of 0.2–0.5 mg/kg body weight/day. In group A and B, treatment was terminated 2 months after clinical improvement (i.e., from 1 to 5 months). In group C treatment was carried out to obtain the recommended total dose of 120–150 mg/kg bw/day. The minimal cumulative dose was 19.90 mg and the maximum was 126.76 mg (group A and B: 19.90 mg and 60.00 mg, respectively; group C 66.67 mg and 126.76 mg, respectively). The mean treatment duration was 6.2 ±1.10 month (range: 3–9 month). These data are summarized in Table 2. There is a statistically significant difference between the treatment time in the examined age groups, i.e. group A versus group B and group A versus group C, and there is no relationship between group B and group C. The test values and significance levels are given in Tables 2 and 3. Eleven different adverse effects were noticed during treatment with isotretinoin. The most common adverse effects are summarized in Table 4. The most common adverse effects observed were dry lips in 90 (100%) participants, followed by perlèche in 24 (40%) participants, retinoid dermatitis in 9 (15%) participants, and xerosis in 7 (11.7%) participants. The only laboratory adverse effect was an increase in the level of total cholesterol observed in 3 (3.33%) participants. All participants were in group C. After cessation of isotretinoin treatment, the patients came for follow-up visits. Patients from groups A and B (60 participants) showed up for a visit after 1 to 8 years. In these groups, 13 people underwent a second acne treatment. In 2 persons (2 girls – 3.33%) the isotretinoin treatment was repeated 2 and 4 years after the end of the initial treatment. Both used 10 mg isotretinoin, at the age of 10 and 11 respectively, for 3 months. Eleven (18.33%) participants required a topical treatment (adapalene cream) only. The remaining participants did not require any medical therapy but might have occasionally used dermocosmetics. Acne scars and post acne hyperpigmentation have not been documented. Among patients from group C (30 participants) 13 underwent a second acne treatment. In 6 participants (20%; 2 girls and 4 boys) the isotretinoin treatment was repeated 11 to 34 months after discontinuation of the initial

Table 1. Statistical analysis 90 children treatment by isotretinoin

Actively	Number of respondents				Percentage			
	Group 1	Group 2	Group 3	Total	Group 1	Group 2	Group 3	Total
City/village: C	30	16	18	64	100.00%	53.33%	60.00%	71.11%
City/village: V	0	14	12	26	0.00%	46.67%	40.00%	28.89%
City/village: Total	30	30	30	90	100.00%	100.00%	100.00%	100.00%
Dose (mg): 10	30	2	0	32	100.00%	6.67%	0.00%	35.56%
Dose (mg): 20	0	28	22	50	0.00%	93.33%	73.33%	55.56%
Dose (mg): 30	0	0	8	8	0.00%	0.00%	26.67%	8.89%
Dose (mg): Total	30	30	30	90	100.00%	100.00%	100.00%	100.00%
Early treatment: no	30	30	9	69	100.00%	100.00%	30.00%	76.67%
Early treatment: yes	0	0	21	21	0.00%	0.00%	70.00%	23.33%
Early treatment: Total	30	30	30	90	100.00%	100.00%	100.00%	100.00%

Table 2. Treatment duration in the examined age groups

Variable	N	Average	Median	Minimum	Maximum	Statistical deviation	Slant
Duration of treatment [month]	30	4.567	5.000	3.000	6.000	0.898	−0.214
Duration of treatment [month]	30	7.000	7.000	5.000	9.000	1.017	0.000
Duration of treatment [month]	30	7.433	7.500	3.000	9.000	1.223	−1.532

Table 3. Duration of treatment in month. Independent variable (grouping)

ANOVA rang Kruskal-Wallis; time of treatment (month)
Independent variable (grouping): Group
Kruskal-Wallis Test: H (2, N = 90) = 53.97256, p < 0.0001
Independent variable (grouping): Prostate
Kruskal-Wallis test: H (3, N = 21) = 13.52684, p = 0.0036

Duration of treatment [month]	Dunn's test			Duration of treatment [month]	Dunn's test		
	From 9–11	From 12–13	From 14–18		From 9–11	From 12–13	From 14–18
From 9–11		5.60	6.75	From 9–11		0.000	0.000
From 12–13	5.60		1.15	From 12–13	0.000		0.752
From 14–18	6.75	1.15		From 14–18	0.000	0.752	

Legend: Kruskal-Wallis Test: H (2, N = 90) = 2.301506, p = 0.3164; (H = 2.3); (p = 0.3164).

therapy (mean: 22.5 ±16.23 months). Thirty (100%) participants required a topical treatment (adapalene cream, clindamycin gel, dermocosmetics) only. Acne scars and post acne hyperpigmentation in this group have been documented in 73.33% of cases. There is no statistically significant difference of the observation time in the examined age groups (Table 5).

Discussion

Acne is a common disease and a lot of patients require treatment for a relatively long time; acne present at any age. The peak incidence of the acne is at puberty, but acne can affect all age groups. Prepubertal acne also occurs, but it is important to recognize as diagnostic and therapeutic procedures differ from pubertal acne. Midchildhood or prepubertal acne raises the suspicion of hyperandrogenemia, further investigations are indicated to rule out underlying disease. Italian findings confirmed that acne prevalence tends to increase with age [6].

Yang *et al.* study in a younger population observed that the prevalence of inflammatory acne in the 7–9 years age group in Taiwan ranged between 1.8 and 3.9% [12]. Napolitano *et al.* showed that acne can frequently appear before puberty (47.5% of girls and 73.6% of boys) [6]. We and other researchers reported that having a higher number of comedones or inflammatory lesions before puberty is linked to subsequent development of severe acne [6, 12, 13]. Preadolescent acne reflects the physiologic awakening of adrenal glands, which usually occurs at 6 to 7 years in girls and 7 to 8 years in boys [14]. Accordingly, levels of DHEA

Table 4. Prevalence of more commonly reported adverse effects (*n* = 90)

Adverse effect	No. of patients (%)
Dry lip	90 (100)
Perlèche	50 (55.56)
Retinoid dermatitis	24 (26,67)
Xerosis	9 (10.00)
Mood change	6 (6,67)
Tiredness	5 (5.56)
Cheilitis	4 (4.44)
Nose bleeds (epistaxis)	3 (3.33)
Bone pain	3 (3.33)
Plentiful menstruation	2 (2.22)
Dry eyes	2 (2.22)

and DHEAS start increasing, and sebaceous gland secretion reactivates.

13-cis-RA (isotretinoin) is the first generation of the nonaromatic retinoids β-carotene (provitamin A) [10]. Oral isotretinoin is unique among acne treatments because it exhibits activity against all major etiologic factors involved in the pathogenesis of acne. Since it was introduced in 1982, oral isotretinoin has revolutionized acne therapy and still is the "Gold standard" in the treatment of acne and its variants. The recommended dose to start isotretinoin therapy is 0.5 mg/kg [15]. The efficacy of systemic retinoid therapy in a number of dermatologic diseases is well established, however, concerns about potential side effects limit their use, especially in children. So it is contraindicated in neonates unless

Table 5. Observation duration in the examined age groups

Variable	N	Average	Median	Minimum	Maximum	Statistical deviation	Slant
Duration of observations [month]	30	33.100	39.500	8.000	50.000	12.896	−0.682
Duration of observations [month]	30	32.700	33.500	5.000	51.000	12.793	−0.516
Duration of observations [month]	30	37.000	38.500	10.000	56.000	14.797	−0.326

the condition is life-threatening (harlequin foetus) [10]. Prolonged therapy requires monitoring of bone structures. A serum triglyceride level occurs commonly with isotretinoin therapy, usually ranging between 2.25 and 4.50 mmol/l. Over the first 4 weeks of treatment, the concentrations of low- and very-low density lipoproteins and cholesterol increase and the level of high-density lipoprotein decreases. The levels then stabilize and return to normal within 8 weeks after treatment is stopped. Therapy should be stopped if the triglyceride level exceeds 8.0 mmol/l because of a risk of pancreatitis [16]. More dramatic increases in the triglyceride level have been observed in patients who were obese, consumed excessive amounts of alcohol, had a family history of hyperlipidaemia or other risk factors [17]. Patients at risk should be put on a low-fat diet and have their alcohol intake limited in an attempt to prevent the triglyceride level from increasing [18]. The retinoids are not stored in the liver, but they are metabolized there; thus the liver is a potential site of toxic effects. The mildly abnormal results of liver function tests sometimes are often corrected while treatment continues and are reversible once it is stopped. Other abnormalities that seem to have had no clinical significance include increases in the peripheral blood platelet count and total protein level and in the urine specific gravity and leukocyte count [17]. Clinical monitoring requires physical examination and laboratory parameters every 4 weeks to manage mucocutaneous or organ adverse effects and ensure compliance, is debatable [19]. The American Academy of Dermatology Consensus concurs with this recommendation for isotretinoin use in acne treatment of adolescents and preadolescents and agrees that it may be used in younger patients with severe, refractory, and scarring acne [20]. Of course, instructions, carer's signatures and counselling about avoiding pregnancies is most desirable.

The oral bioavailability may be enhanced with food. It has half-life of 10–20 h, and is completely cleared from the body with 1 month of stoppage of the drug. Adverse drug reactions are common by oral isotretinoin and one cannot predict their occurrence. Most idiosyncratic drug reactions are thought to be caused by chemically reactive metabolites, and the skin is a frequent site of idiosyncratic reactions [21]. The most common side-effects of systemic isotretinoin administration are dry mucous membranes, nose bleed, and dry skin. Brzezinski et al. in their study observed dry lips as the most commonly reported adverse effect, affecting 100% of users, followed by xerosis (94.97%) and facial erythema (66.21%). Of all adverse effects, psychiatric symptoms accounted for 5.16%; while eye lesions accounted for 8.96% [22]. In our study, the following was most often observed: dry lips, perlèche, retinoid dermatitis, occurring respectively in 100%, 55.56%, and 26.67%. In lab investigations an increase in the level of total cholesterol and serum triglycerides was noticed [22, 23]. In our 90 patients we observed only an increase in the level of total cholesterol in 3 participants. Three of the most significant and controversial groups of adverse effects attributed to isotretinoin and described in the drug's package insert are skeletal issues; potential for development of inflammatory bowel disease (IBD); and mood changes, depression, suicidal ideation, and suicide [24]. In a big study by Brzezinski et al. (3,525 participants), authors noticed mood changes in 9.50%, suicidal ideation in 0.02% [22]. The last study by authors from Brazil using databases from July 2017 to March 2018 described that only one serious adverse event was reported in the isotretinoin group; however, isotretinoin may result in more minor adverse effects [25]. None of the studies in this comparison reported serious adverse effects. There is a certain relationship between the patient's age and the recurrence of the disease [1, 26].

It mainly referred to the old child. Statistical analysis has proved that there existed a significant relationship between the recurrence of the disease analysed and the patient's sex. A little higher rate of illness occurrence can be observed in the female group. The psychological consequences of acne are widely described. As a particularly visible skin disorder, acne complicates the daily lives of adolescents who are undergoing multiple transformations: physical, intellectual and emotional. While it is well established that acne can be responsible for depression and low self-esteem, it is likely that this impact is aggravated by the sociological evolution of adolescents in the 21st century [27]. Authors from France in a two-centre retrospective study analysed infantile acne in 16 cases [28]. Nine had a family history of severe adolescent acne. Two patients had been effectively treated with oral isotretinoin. Napolitano et al. out of 683 children (mean age: 11.05) described acne in 34.3% [6]. The prevalence increased with age being higher after 13 years of age. The result of untreated and late-treated acne are post inflammatory hyperpigmentation and scars as effect severe acne has healed. It may take years to disappear if

acne is not properly treated immediately. Squeezing the acne spread infection up to dermis. The deeper the infection, the darker the pigmentation will be.

Conclusions

As acne in childhood may persist over many years, early control may help to minimize its impact on patients. Available published data regarding multiple outcomes for early intervention in acne are scarce [29]. Early, reasonable and short-term use of isotretinoin seems to reduce the incidence of acne in the future. Comfortable functioning in the society is important [30]. The financial benefits are also flowing from this. Secondary acne symptoms (scars, hyperpigmentation) can be minimized. However, even wider and multi-centre studies are needed.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

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