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Evaluation of the gastrointestinal findings of nodulocystic acne patients during systemic isotretinoin therapy

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Background/aim: Systemic isotretinoin treatment is an effective treatment modality for nodulocystic acne, the clinical use of which has been associated with reports of adverse events. We conducted a prospective study with the aim of determining the possible gastrointestinal and laboratory findings of nodulocystic acne patients during systemic isotretinoin treatment.

Materials and methods: Seventy patients with nodulocystic acne completed the study. During the monthly follow-up visits, liver function tests and lipid profiles of the patients were evaluated and gastrointestinal system complaints were examined.

Results: We recorded a significant elevation in liver function tests and lipid profiles of the patients, the most prominent elevation being in plasma triglyceride concentrations. We observed that nausea, dyspepsia, abdominal pain, and diarrhea were the rare gastrointestinal symptoms encountered during systemic isotretinoin therapy. Constipation and anorectal bleeding were relatively more common symptoms and there seemed to be a relation between these two symptoms.

Conclusion: Our study is the first to analyze the gastrointestinal findings of patients during systemic isotretinoin treatment. Dermatologists and gastroenterologists must keep in mind that, as well as known laboratory findings like hypertriglyceridemia and elevated liver function tests, systemic isotretinoin therapy may also cause significant clinical gastrointestinal findings.

Key words: Acne vulgaris, isotretinoin, adverse effects

1. Introduction

Acne is a chronic inflammatory disease of the pilosebaceous unit resulting from androgen-induced increased sebum production, altered keratinization, inflammation, and bacterial colonization of hair follicles on the face, neck, chest, and back by *Propionibacterium acnes* (1). It is a common disease of adolescence and young adulthood.

Targeting of the major pathogenetic factors, depending on clinical type and severity, represents the most effective approach to treat acne (2). Systemic isotretinoin as a monotherapeutic agent strongly affects all four major pathogenetic factors and it is the most effective medication resulting in clinical cure in around 85% of cases (1,2). Isotretinoin is usually reserved for severe nodulocystic scarring acne or acne resistant to other therapies (1).

The clinical use of oral isotretinoin has been associated with reports of adverse events with various implications for the patient. The most common adverse reactions associated with oral isotretinoin are the mucocutaneous effects (3). Cheilitis is the dominant gastrointestinal adverse reaction and makes the gastrointestinal system the body system with the highest frequency of adverse events (3). Nausea, vomiting, gastric ulcers, abdominal pain, and inflammatory bowel disease have previously been reported in the literature (4).

We conducted a prospective study with the aim of determining the possible gastrointestinal and laboratory findings of nodulocystic acne patients during systemic isotretinoin treatment.

2. Materials and methods

Seventy patients with nodulocystic acne who had been admitted to our outpatient dermatology clinic completed the study over a period of 2 years. Our institutional review board approved the project, and informed consent was appropriately obtained from each participant.

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The nodulocystic acne patients for whom systemic isotretinoin treatment was planned and whose basal complete blood count, biochemistry, and lipid profiles were within normal limits were included in the study. Female patients were also evaluated for human chorionic gonadotropin (β-hCG) levels during the basal laboratory investigation. Patients who were younger than 18 years old and patients with a history of hyperlipidemia, diabetes mellitus, hepatitis, pancreatitis, or inflammatory bowel disease were excluded from the study. The systemic isotretinoin treatment was continued for 6–8 months for each patient with an initiation dose of 0.5 mg kg^{-1} day^{-1} and a cumulative dose of 150 mg kg^{-1}.

During the monthly follow-up visits liver function tests and lipid profiles of the patients were evaluated and gastrointestinal system complaints including nausea, vomiting, abdominal pain, dyspepsia, diarrhea, constipation, and bloody stool were examined. If the patient had a significant complaint or if there was an abnormality in the laboratory values, the patient was sent to consult with the gastroenterology department.

2.1. Statistics

Descriptive statistics are presented as frequency, percentage, and median (min–max) values. Categorical data (sex, age, nausea, vomiting, dyspepsia, abdominal pain, diarrhea, constipation, bleeding) were compared by Fisher's exact test. Continuous data were tested for normality by histograms, p-p plots, and the Kolmogorov–Smirnov test. The continuous variables before and after treatment were compared by the Wilcoxon signed-ranks test. Percentage of changes in liver function test and lipid profile were calculated for each value as [(maximum value – basal value) / basal × 100]. All comparisons were made for a two-tailed significance level of 0.05.

3. Results

Seventy patients completed the study. Of these 70 patients, 54 were female (77.1%) and 16 were male (22.9%). The median age of the patients was 22 (18–33) years.

Reports of gastrointestinal complaints in any period of the treatment were 6.89 times higher in female patients (n = 17) than male patients (n = 1) [OR: 6.89 (95% CI: 0.82–151.09)], but this was not statistically significant according to Fisher's exact test (P = 0.053).

Frequency and percentage of the patients exceeding normal values in terms of laboratory results in any period of the treatment were as follows: alanine aminotransferase (ALT), nine patients (12.9%); aspartate aminotransferase (AST), four patients (5.7%); gamma-glutamyl transferase (GGT), two patients (2.9%); triglyceride (TG), 20 patients (28.6%); low-density lipoprotein (LDL), 46 patients (65.7%); and total cholesterol (T-chol), 14 patients (20%). Reference intervals are as follows: ALT, 7–35 U/L; AST, 13–41 U/L; GGT, 7–64 U/L; TG, <150 mg/dL; LDL, 0–100 mg/dL; T-chol, 0–200 mg/dL.

Comparison of the basal laboratory values with the maximum laboratory values recorded during the treatment revealed that there was a significant change in each parameter of liver function tests and lipid profiles that could be attributed to isotretinoin treatment (Wilcoxon signed-ranks test, P < 0.05) (Table 1).

According to evaluation of the percentage of change in laboratory values due to isotretinoin treatment, TG was the leading parameter with the highest percentage of change [median: 77.54 mg/dL (range: 0–478.43)] (Table 2).

There was no significant difference between the patient group that was asymptomatic and that with at least one symptom in terms of percentage of change of laboratory values before and after treatment (Mann–Whitney U test, P > 0.05).

Table 1. Comparison of the basal laboratory values with the maximum laboratory values recorded during the treatment.

	Basal	Maximum	P-value [a]
	Median (min–max)	Median (min–max)	
ALT (U/L)	15 (10–38)	19 (12–93)	0.0001
AST (U/L)	19 (11–41)	24 (16–107)	0.0001
GGT (U/L)	15.5 (7–61)	20.5 (11–77)	0.0001
TG (mg/dL)	61 (9–153)	107 (18–363)	0.0001
LDL (mg/dL)	85 (52–114)	112 (59–166)	0.0001
T-chol (mg/dL)	145 (102–200)	175 (113–243)	0.0001

Reference intervals: ALT, 7–35 U/L; AST, 13–41 U/L; GGT, 7–64 U/L; TG, <150 mg/dL; LDL, 0–100 mg/dL; T-chol, 0–200 mg/dL.
[a] Wilcoxon signed-ranks test.

Table 2. Percentage of change in laboratory values due to isotretinoin treatment [(maximum value – basal value) / basal × 100].

	Median	Minimum	Maximum
ALT	25.00	0	575.00
AST	28.99	0	723.08
GGT	36.60	0	285
TG	77.54	0	478.43
LDL	29.31	0	98.59
T chol	17.95	0	66.44

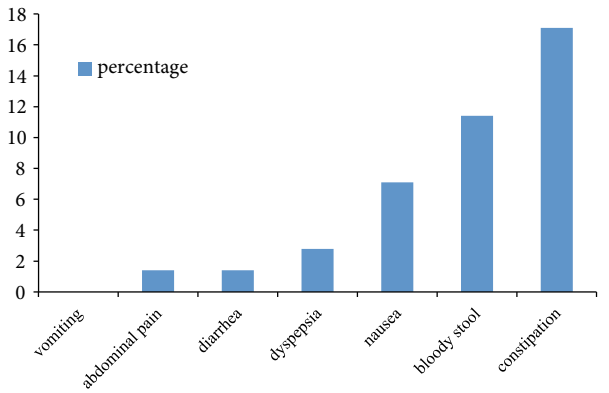

Figure. Percentage of gastrointestinal symptoms.

Constipation was the leading gastrointestinal symptom among the patients. Twelve out of 70 (17.1%) patients reported constipation during the oral isotretinoin treatment. Three patients with complaints of constipation reported that constipation was present before the treatment. Nevertheless, in two of these three patients, it was intensified by the isotretinoin treatment. Bloody stool was the second most common symptom at 11.4% (8/70). Nausea was the next most common symptom at 7.1% (5/70). Two patients (2.8%) reported dyspepsia that appeared after the isotretinoin treatment and one of them stated that the complaint continued throughout the isotretinoin treatment. Abdominal pain and diarrhea were each reported in only one patient (Figure).

When we evaluated the relation between constipation and bloody stool, four of 12 patients who complained about constipation also had bloody stool. Furthermore, out of the eight patients who reported bloody stool during isotretinoin treatment, four of them also reported constipation. According to the kappa measure of agreement test there was a weak consistency between constipation and bloody stool complaints that was significant statistically (kappa: 0.305, $P < 0.05$).

Two patients were examined with rectosigmoidoscopy due to the complaint of bloody stool, which appeared during isotretinoin treatment. Constipation was the accompanying complaint of bloody stool in both cases. The results of the rectosigmoidoscopy examinations were anal fissure in one of the patients and hemorrhoid with hypertrophic anal papilla in the other.

Two patients were diagnosed with irritable bowel syndrome (IBS); one of them was diagnosed during isotretinoin treatment with the complaint of constipation and the constipation ended 2 weeks after the completion of the isotretinoin treatment. The other patient was diagnosed with IBS with the complaints of nausea and diarrhea 2 months after the completion of the isotretinoin treatment, although she did not have any symptoms during the treatment. The patients with IBS were diagnosed using the Manning criteria, which focus on pain relieved by defecation, having incomplete movements, mucus in the stool, and changes in stool consistency.

4. Discussion

The clinical use of oral isotretinoin has been associated with reports of adverse events with various implications for the patient. Since isotretinoin (13-cis-retinoic acid) is a vitamin A (retinol) analog, side effects seen with this drug are similar to the clinical findings in hypervitaminosis A syndrome. Gastrointestinal findings of hypervitaminosis A syndrome are anorexia, nausea, abdominal pain, and cirrhosis. Elevated triglycerides, cholesterol, and liver function tests are the laboratory abnormalities that can be seen in hypervitaminosis A (5).

The liver is the principal storage site for vitamin A (retinol) and excessive ingestion of vitamin A results in liver disease leading to cirrhosis. Vitamin A-induced hepatic injury apparently results from the intrinsic toxicity of vitamin A, and the extent of the injury depends on the dose and duration of exposure. Elevations of aminotransferases are found in over 70% of patients with vitamin A-induced liver injury (6).

Retinoids act by regulating the expression of the genes that control lipoprotein metabolism at both the transcriptional and posttranscriptional levels. Dyslipidemia, characterized by increased TG and T-chol levels and lowered high-density lipoprotein (HDL) plasma concentrations, is a common side effect of retinoid therapy (7). Although a causal relationship between long term retinoid therapy and chronic liver toxicity has not been demonstrated yet, hepatitis is a well-known gastrointestinal side effect of retinoid therapy. Nonetheless, significant hepatitis is reported to occur more commonly with retinoids other than isotretinoin (5).

The most common systemic side effect of retinoid therapy is an increase in the plasma TG concentrations.

Overt hypertriglyceridemia develops in 20% of patients who are treated with retinoids in addition to concomitant increases of T-chol and LDL cholesterol levels and decreases of HDL levels (7). Elevated liver function test results (and especially the transaminases) occur in 15% of patients during isotretinoin therapy (5). Once the treatment is stopped, increases in liver function tests and TG values generally return to normal within 2–4 weeks (3,8). The results of our study correlated with the known systemic side effects of retinoid therapy. There was a significant elevation in liver function tests and lipid profile, the most prominent elevation being in plasma TG concentrations.

The most common adverse reactions associated with oral isotretinoin are the mucocutaneous effects on the lips, eyes, mouth, and other epidermal surfaces (3,9). Nonspecific gastrointestinal complaints of nausea, diarrhea, and abdominal pain have been reported with isotretinoin therapy but are uncommon (5). In our study, abdominal pain and diarrhea were the least common complaints, each being reported by only one patient. Dyspepsia and nausea were more common than these but were still not significant.

Among the possible gastrointestinal adverse effects of isotretinoin, the most remarkable one is inflammatory bowel disease (IBD). Since the first detailed report of an association of oral isotretinoin therapy with IBD by Brodin (10) in 1986, a total of 12 cases of isotretinoin-related IBD have been reported in the English literature (11–13). Many studies concerning the relationship between isotretinoin and IBD have been conducted, but there is no concordance between their results (14). Reddy et al. concluded that in a subgroup of patients, isotretinoin might serve as a trigger for IBD (15). Crockett et al. in their first study in 2009 mentioned that evidence was insufficient to confirm or refute a causal association, while in their second study they claimed that ulcerative colitis but not Crohn disease was associated with previous isotretinoin exposure (16,17). Unlike the former studies, Bernstein et al. concluded that isotretinoin exposure was not associated with an increased risk of developing IBD (18). The results of the metaanalysis by Etminan et al. did not suggest an increase in the risk of IBD with the use of isotretinoin (19). The outcome of the study of Alhusayen et al. was that IBD was not related with isotretinoin. Moreover, they stated that the risk of IBD after topical acne medication was similar to the risk of isotretinoin and they suggested a possible association between IBD and acne (20). The data from an in vivo study evaluating the effects of retinoids in mouse models of IBD provided no evidence for a detrimental effect of retinoid treatment on intestinal inflammation (21). In a recent population-based case-control study by Racine et al., isotretinoin use was not associated with increased ulcerative colitis risk, but it was associated with decreased Crohn disease risk (22).

Although the relationship between isotretinoin treatment and IBD has not been clarified yet, the data from the recent studies do not support a correlation between isotretinoin and IBD. None of our patients were diagnosed with IBD during isotretinoin treatment.

Anal fissure and rectal bleeding are the rarely reported side effects of isotretinoin. The reported patients usually complained of anal pain and rectal bleeding and some of them declared that these symptoms were intensified by defecation. Anal fissure is the common finding of all such patients in examination. The possible mechanism of anal fissure formation and rectal bleeding was explained by tearing of the xerotic anal mucosa due to trauma, such as forceful defecation (23–25).

In our study, bloody stool, which can be accepted as a sign of anorectal bleeding, was the second most common gastrointestinal symptom among our patients. Out of eight patients two were examined by rectosigmoidoscopy and the results were anal fissure and hemorrhoid with hypertrophic anal papilla, respectively. Both of these patients also had constipation symptoms. When we evaluated the relation between constipation and bloody stool, half of the patients who reported bloody stools also reported constipation. There is a weak consistency between the two complaints that is significant statistically. We suggest that constipation may be the triggering factor in the case of a dry and delicate mucosa, as a result of isotretinoin therapy, for those patients who report bloody stool.

Our study is the first to analyze both the gastrointestinal findings and the laboratory findings of patients during systemic isotretinoin treatment. We observed that nausea, dyspepsia, abdominal pain, and diarrhea were the rare gastrointestinal symptoms that can be encountered with systemic isotretinoin therapy. Constipation and anorectal bleeding were relatively more common symptoms and there seems to be a relation between them. In conclusion, both dermatologists and gastroenterologists must keep in mind that, as well as the known laboratory findings like hypertriglyceridemia and elevated liver function tests, systemic isotretinoin therapy may also cause the aforementioned clinical gastrointestinal findings.

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