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Isotretinoin is a Safety Therapy on Kidney: A Retrospective Study

İsotretinoin Böbrekler Üzerinde Güvenli Bir Tedavidir: Geriye Dönük Bir Çalışma

Abstract

Objective: Isotretinoin is widely used in severe acne treatment. The drug leads to several adverse effects; skin and mucous membranes are frequently affected. It may also cause serious and fatal adverse effects like kidney damage. The aim of this study is to determine the safety of isotretinoin usage on kidney functions in patients with acne vulgaris.

Methods: Eighty six patients with severe acne vulgaris and receiving 0.5 mg/kg/day of isotretinoin treatment were included in the study and evaluated retrospectively. Serum urea, creatinine, complete blood count, aspartate aminotransferase, alanine aminotransferase, lipid profile datas were obtained from patient files. Glomerular filtration rate (GFR) was measured at the baseline of treatment, 3rd and 6th months of treatment.

Results: We detected significant increases in levels of creatinine on the third month (p=0.041), but it was not clinically significant, and there was no significant difference in creatinine levels at 6th month. There were no significant differences among the baseline, 3rd month (p=0.066) and 6th month (p=0.429) of GFR values.

Conclusion: We think that isotretinoin is safe for the kidneys but patients with high creatinine levels at the baseline of treatment should be closely followed up.

Keywords: Isotretinoin, acne vulgaris, creatinine, urea, kidney function, modification of diet in renal disease

Öz

Amaç: Şiddetli akne tedavisinde isotretinoin yaygın olarak kullanılmaktadır. İlaç çok sayıda yan etki oluşturmaktadır; deri ve mukoz membranlar ise sıklıkla etkilenmektedir. Ayrıca böbrek hasarı gibi ciddi ve ölümcül yan etkiler de görülebilmektedir. Bu çalışmanın amacı, akne vulgarisli hastalarda isotretinoin kullanımının böbrek fonksiyonları üzerindeki güvenilirliğini değerlendirmektir.

Yöntemler: Şiddetli aknesi olan ve 0,5 mg/kg/gün isotretinoin tedavisi alan 86 hasta çalışmaya alındı ve geriye dönük değerlendirildi. Serum üre, kreatinin, tam kan sayımı, aspartat aminotransferaz, alanin aminotransferaz, lipit profil verileri hasta dosyalarından elde edildi. Glomerüler filtrasyon hızı (GFR) tedavi başlangıcında, tedavinin 3. ve 6. ayında hesaplandı.

Bulgular: Tedavinin 3. ayında kreatinin değerlerinde anlamlı artış gözlendi (p=0,041); ancak klinik olarak anlamlı değildi, tedavinin 6. ayında ise kreatinin değerlerinde anlamlı farklılık yoktu. Başlangıç, 3. ay (p=0,066) ve 6. ay (p=0,429) GFR değerleri arasında anlamlı farklılık görülmedi.

Sonuç: İsotretinoinin böbrekler için güvenilir olduğunu düşünüyoruz; ancak tedavi başlangıcında kreatin değeri yüksek olan hastalar yakın takip edilmelidir.

Anahtar kelimeler: İsotretinoin, akne vulgaris, kreatinin, üre, böbrek fonksiyonu, böbrek hastalığında diyet modifikasyonu

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Introduction

Acne is one of the most general disorder treated by dermatologists. The main symptoms include comedones, papules, pustules, nodules, cysts and scars in acne vulgaris. The aetiology of acne vulgaris remains poorly known. The current view is that acne is related to factors such as androgen, hyper-seborrhoea, hyperkeratosis of the pilosebaceous ducts, follicular orifice blockage, and proliferation of bacteria (1,2). Treatment of acne depends on its severity. Topical or systemic treatments such as oral antibiotics and oral isotretinoin could be chosen according to acne severity. Isotretinoin was proven by the Food and Drug Administration for the treatment of severe acne and has the potential to effect all of the pathogenetic pathways on acne (2-4).

Oral isotretinoin is a derivative of vitamin A, which acts as a synthetic isomer of retinoic acid (3-5). Its effect depends on sebocyte apoptosis, which results from isotretinoin-induced expression of the apoptotic protein tumour necrosis factor inducing ligand, insulin-like growtha factor-binding protein-3 (5). It frequently has mucocutaneous side effects. The other side effects are elevated liver enzymes, calcifications, hyperlipidemia, arthralgia, myalgia, minor and major depression and rarely psychosis. It has been reported that these side effects are dose-dependent (2,4,6,7).

There are some reports that isotretinoin had toxic effects such as hyperuricemia, acute kidney injury, interstitial nephritis and Nephritic Syndrome (8-13). Severe rhabdomyolysis with mortal outcome was reported with using the drug (8). However, there are some case reports which reported that isotretinoin could induce renal damage, some authors suggested that isotretinoin use is safe in renal transplant and haemodialysis patients (14-17). To our recognition, our study is the first study that investigated the renal functions while using isotretinoin treatment for acne vulgaris.

Materials and Methods

Study Population

A total of 86 patients with acne vulgaris treated with 0.5 mg/kg/daily isotretinoin (Roaccutane, Roche Diagnostics, Switzerland) were included into the study retrospectively. The mean age was 21.4±5.5 (16-43 years). Female/male ratio was 56 (65.1%)/30 (34.9%). Fifty-five patients were treated with isotretinoin for at least 4 months. Each patient's medical records were evaluated from the patient's files.

All laboratory parameters including complete blood count, aspartate aminotransferase, alanine aminotransferase, urea, creatinine, lipid profiles (Abbott Architect c8000, USA) at baseline, before initiating isotretinoin were normal. Glomerular filtration rate (GFR) were measured at baseline, 3rd and 6th months of treatment. GFR was assessed by simplified modification of diet in renal disease (MDRD) procedure (mL/min/1.73 m^2).

Exclusion of patients were as follows: 20 of 32 patient had been discontinued the therapy when used the therapy for 3 months on their own request. Twelve of 32 had been excluded from the study because of using non-steroidal anti-inflammatory drugs and antibiotics for other general problems such as pyoderma, infections. There were no patients that excluded for isotretinoin side effects such as liver, kidney or blood abnormalities. Data were recorded from patients' files on hospital data information system. Approval for the study was obtained from the Yıldırım Beyazıt University Yenimahalle Training and Research Hospital Ethic Committee (2016-41). Informed consent was obtained from all participants included in the study.

Laboratory Data

Serum urea, creatinine (Abbott Global Healthcare and Research, USA), GFR were recorded from patient's file, at baseline. And then after 3 and 6 months of treatment. Fifty-five patients continued the therapy for 6 months at the cumulative dose of 120 mg/kg based on weight. Estimated GFR (eGFR) was assessed by MDRD (mL/min/1.73 m^2). The study was approved by the Ethical Committee of Yıldırım Beyazıt University Yenimahalle Training and Research Hospital and was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Whether the distribution of continuous variables was normal or not was assessed by Kolmogorov-Smirnov test. While the continuous variables were indicated as mean ± standard deviation or median (minimum-maximum), otherwise, number of cases and percentages were used for categorical data. The comparison of baseline and 3rd month measurements were performed by Wilcoxon signed-rank test. The Friedman test was applied for determining the differences among more than two measurement time points. Data analysis was performed by using IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, New York, USA). A p value less than 0.05 was considered statistically significant.

Results

Demographic characteristics and the frequency values at initial and 3rd month are shown in Table 1. The frequency values at initial and 3rd month and 6th month are shown in Table 2. We detected increases in levels of creatinine on the third month, it was statistically different (p=0.041) but this was not clinically important and there were no statistically differences between third month and six months values of creatinine (p=0.366). There were no statistically differences between initial and 3rd month values of urea (p=0.305) and, between initial and 3rd month values of eGFR (p=0.066) (Table 3).

The kidney function was accepted as normal or high if eGFR ≥90. There was no statistically significant difference between the urea values of 3rd month and 6th month (p=0.965). There was no statistically significant difference between the urea values at baseline, 3rd month and 6th month (n=55, p=0.366). There was no difference between urea, creatinine and eGFR, at baseline, 3rd and 6th month levels respectively (p=0.965, p=0.366 and p=0.429) (Table 4).

Discussion

We detected increases in levels of creatinine on the third month (p=0.041) but this was not clinically important and there were no statistically significant differences between

the third and six months values of creatinine (p=0.366). There were no statistically significant differences between the values of baseline urea, third month urea (p=0.305) and six months urea values and between the values of GFR of 3rd month (p=0.066) and 6th month (p=0.429) (Table 2).

GFR is the most widely-used method of determinate the level of kidney function. The Kidney Disease: Improving Global Outcomes is a guideline to detect degree of chronic kidney deficiency (18). It is recommended that in patients with eGFR <60 mL/min/1.73 m^2, urine protein assessment and a repeat measurement of kidney function be undertaken. If the low eGFR is likely long term, the repeat assessment could be in 3 months, which would meet the criteria for chronic kidney disease (CKD). Low GFR could be acute or subacute, the repeat assessment should be made sooner, sometimes within days depending on the clinical situation to diagnosed the kidney damage. If eGFR is 60-89 mL/min/1.73 m^2 it is defined as mildly decreased GFR and it is offered that the patient should be follow up about clinical presentations. CKD is defined as abnormalities of kidney structure or function, present for 3 months, with implications for health (19). In our study, there were only three patients whose GFR <90 at 3rd month of isotretinoin treatment but it was not defined as kidney injury in the literature, they were female and their creatinine level

Table 1. Demographic and the laboratory values of study group (n=86) at initial and at 3rd month

	Initial	3rd month	p value†
Demography			
Gender, M/F n (%)	30 (34.9)/56 (65.1)	30 (34.9)/56 (65.1)	NS
Age, year	21.4±5.5	21.4±5.5	NS
Biochemistry			
Urea, mg/dL	23.1±6.8	22.4±6.7	0.305
Creatinine, mg/dL	0.74±0.09	0.75±0.09	0.041
GFR, mL/min	118.6±16.4	117.0±15.5	0.066

GFR: Glomerular filtration rate, NS: None significant, M: Male, F: Female
†Wilcoxon signed-rank test
All data are given as means ± standard deviations

Table 2. Comparison of initial, 3rd and 6th month laboratory measurements (n=55)

	Initial	3rd month	6th month	p value†
Urea, mg/dL	23.0±6.3	22.5±5.8	22.6±5.4	0.965
Creatinine, mg/dL	0.73±0.09	0.74±0.08	0.73±0.07	0.366
eGFR, mL/min	117.7±16.1	116.1±14.6	117.4±14.3	0.429

eGFR: Estimated glomerular filtration rate
†Friedman test
All data are given as means ± standard deviations

Table 3. The laboratory values at initial of the treatment and at the 3rd month (n=86)

Variables	Initial	3rd month	p value†
Urea, mg/dL	22.0 (13.0-45.0)	22.0 (10.0-44.0)	0.305
Creatinine, mg/dL	0.73 (0.57-1.05)	0.73 (0.59-1.06)	0.041
eGFR*	118.4 (80.9-171.1)	115.2 (83.2-157.9)	0.066

eGFR: Estimated glomerular filtration rate
†Wilcoxon signed-rank test
*Estimated glomerular filtration rate: (mL/min/1.73m^2)
All data are given as median (range)

Table 4. The laboratory results of the patients (n=55) according to 6 month follow up

Variables	Initial	3rd month	6rd month	p value†
Urea	22.0 (13.0-45.0)	22.0 (12.0-33.0)	21.0 (11.0-37.0)	0.965
Creatinine	0.73 (0.57-1.05)	0.72 (0.61-0.99)	0.72 (0.61-0.90)	0.366
eGFR*	119.9 (80.9-171.1)	114.5 (83.2-157.3)	117.1 (83.5-150.5)	0.429

eGFR: Estimated glomerular filtration rate
†Friedman test
*Estimated glomerular filtration rate: (mL/min/1.73m^2)

was normal. One patient of 3 had not been completed the therapy on her own on the 4th month of the therapy. Two patients had been had low GFR levels. This might be due to that they are female and muscle density was low. This low eGFR levels was not clinically important because there was no clinic about kidney injury.

There are conflicting reports about safety of oral isotretinoin on kidneys. Some authors reported that it may be toxic (9-13). Some authors suggested that it is safe on kidneys (14-17). Kaya Aksoy et al. (11) had been reported that isotretinoin may cause drug-related acute tubulointerstitial nephritis. In this case report, a patient was diagnosed with acute tubulointerstitial nephritis. Pathological signs of renal biopsy sections had been revealed interstitial mononuclear cell and eosinophilic infiltration in this case (11). Armaly et al. (10) had been reported a 17-year-old female who experienced acute kidney injury to using isotretinoin. She was diagnosed as acute interstitial nephritis. In this report, the patient had been used oral isotretinoin 2 years ago and then restarted the same drug again. Two months later after initiating oral isotretinoin, the patient's creatinine was calculated 2 mg/dL and then the drug had been stopped. Two weeks later her kidney function had been returned to normal values (10).

Sarifakioglu et al. (13) reported a case who developed hematuria after treatment with isotretinoin. Yesilkaya et al. (20) were conducted a study which investigated the frequency of hematuria while using isotretinoin. They found the frequency of hematuria 17% but this frequency was not different from that of the normal population. The authors suggested that hematuria seen secondary to isotretinoin treatment is due to mucosal dryness in the urinary system (20).

It was suggested that apoptosis may be the underlying mechanism of the possible side effects of the drug on hippocampal neurons, epidermal keratinocytes and mucosa cells, skeletal muscle cells, and hepatocytes. Genetic variants of components of the apoptotic signaling cascade, might explain variations in the severity of isotretinoin-induced apoptotic signaling and determine subgroups of patients who experience either stronger adverse effects with the therapy (5). Isotretinoin-induced apoptotic signaling might trigger the nephritis on those patients to related with genetic pattern isotretinoin therapy as suggested by Melnik (5) and those side effects could not predict before isotretinoin therapy. The influence of retinoids on kidneys of acne patients seems to be multifactorial such as an unknown immune modulation and direct podocyte damage in some patients.

Some authors suggested that isotretinoin is not safe for kidney in patients with lupus nephritis (LN) and Nephritic syndrome (9-11). But despite all this case reports Miziolek et al. (17) reported a review and suggested benefits of isotretinoin therapy for patients with kidney diseases. Miziolek et al. (17) concluded that isotretinoin can use safely for acne treatment in patients whose diagnosed as LN.

It was asserted that retinoids affect mononuclear cell infiltrations of renal tissue and it may trigger glomerular damage. It has also been presented that retinoids affects the synthesis of different cytokines interleukin (IL)-2, IL-12, interferon-gamma, IL-4, IL-10. It was thought that retinoids can regulate the production of vasoactive substances in the kidney (21-23). Interstitial fibrosis is the main cause of end stage renal failure. Retinoids are believed to inhibit inflammatory and proliferative pathways (24-28). Lehrke et al. (25) suggested that the natural retinoic acid and 13-cis retinoic acid conserve renal formation and function in rat mesangioproliferative glomerulonephritis and that all retinoid agonists with different subtypes are profoundly efficient in reducing renal damage and proliferation of mesangial cells.

In some reports, it was reported that creatinine phosphokinase (CPK) may be risen while using isotretinoin with or without muscle-related complain. Some authors offered to measure the CPK levels as well as renal tests for cases who complaining with pain (29,30). But in literature only one patient was reported die due to severe rhabdomyolysis while using isotretinoin (8). Yildizgoren et al. (31) reported a study that investigate the effect of isotretinoin on muscle. Isokinetic measurements had been obtained from the hamstring and quadriceps on the non-dominant side of the body at baseline and 3-month follow-up using an isokinetic dynamometer. They suggested that systemic isotretinoin did not significantly alter muscle strength, fatigue, and endurance (31).

McDonald et al. (14) and Jung et al. (16) presented cases of cyclosporine-induced sebaceous hyperplasia in renal transplant recipients, profitably treated with isotretinoin. In this case reports, all of the three patients tolerated isotretinoin well, with no exchange in graft function. The authors suggested that the drug is safety in the treatment of cyclosporine-induced sebaceous hyperplasia (14,16).

Witt et al. (28) also suggested that retinoic acid may be a novel non-toxic treatment on kidneys and may be an option for nephroblastomatosis in children.

Demirseren et al. (21) suggested that the adverse effects that may occur in the first 4 weeks during isotretinoin. Because of kidney, liver functions, complete blood count offered to done before starting the treatment by authors (21).

In our study, there were no patient that had several side effects during the therapy. There was also no adverse effect on kidney. Each visit patient's must be asked about if is there any severe compliant like severe pain, back pain and physical examination must be done such as leg edema. We suggest that kidney functions may be done before starting isotretinoin therapy and the first month after initiating and then if there were no kidney abnormalities it is not necessary to study kidney functions again.

Conclusion

The severe side effects of isotretinoin may occur incidentally and may be due to apoptosis or genetic factors which are not known yet. We suggest that isotretinoin is a safe therapy.

Ethics

Ethics Committee Approval: The study was approved by the Ethical Committee of Yıldırım Beyazıt University Yenimahalle Training and Research Hospital (2016-41) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all participants included in the study.

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Authorship Contributions

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References

1. Das S, Reynolds RV. Recent advances in acne pathogenesis: implications for therapy. Am J Clin Dermatol 2014;15:479-88.
2. İzol B, Başkan E, Başar Z, ve ark. Orta Şiddette Akne Vulgaris Tedavisinde Aralıklı Düşük Doz İzotretinoin Tedavisi. Turk J Dermatol 2012;6:7-12.
3. Zaenglein AL, Pathy AL, Schlosser BJ . Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol 2016;74:945-73.
4. Hansen TJ, Lucking S, Miller JJ. Standardized laboratory monitoring with use of isotretinoin in acne. J Am Acad Dermatol 2016;75:323-8.
5. Melnik BC. Apoptosis May Explain the Pharmacological Mode of Action and Adverse Effects of Isotretinoin, Including Teratogenicity. Acta Derm Venereol 2017;97:173-81.
6. Ertam I, Alper S, Unal I. Is it necessary to have routine blood tests in patients treated with isotretinoin? J Dermatolog Treat 2006;17:214-6.
7. Kizilyel O, Metin MS, Elmas OF, et al. Effects of oral isotretinoin on lipids and liver enzymes in acne patients. Cutis 2014;94:234-8.
8. Hartung B, Merk HF, Huckenbeck W, et al. Severe generalised rhabdomyolysis with fatal outcome associated with isotretinoin. Int J Legal Med 2012;126:953-6.
9. van Oers JA, de Leeuw J, van Bommel EF. Nephrotic syndrome associated with isotretinoin. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2000;15:923-4.
10. Armaly Z, Haj S, Bowirrat A, et al. Acute kidney injury following isotretinoin treatment. Am J Case Rep 2013;14:554-6.
11. Kaya Aksoy G, Koyun M, Akkaya B, et al. Eosinophilic tubulointerstitial nephritis on treatment with isotretinoin. Eur J Pediat 2016;175:2005-6.
12. Solak B, Erdem T, Solak Y. Isotretinoin use for acne vulgaris is associated with increased serum uric acid levels. J Dermatolog Treat 2016;1-4.
13. Sarifakioglu E, Yilmaz AE, Erpolat S. Terminal hematuria associated with oral isotretinoin treatment in a patient with acne vulgaris. Pediatric dermatology 2012;29:668-9.
14. McDonald SK, Goh MS, Chong AH. Successful treatment of cyclosporine-induced sebaceous hyperplasia with oral isotretinoin in two renal transplant recipients. Australas J Dermatol 2011;52:227-30.
15. Montagnac R, Reguiai Z, Bressieux JM, et al. [Value of isotretinoin in the treatment of acne in hemodialysis patients: apropos of 1 case]. Nephrologie 2003;24:101-5.
16. Jung HY, Kim M, Cho BK, et al. A Case of Cyclosporine-Induced Sebaceous Hyperplasia in a Renal Transplant Patient Successfully Treated with Isotretinoin. Ann Dermatol 2016;28:271-2.
17. Miziolek B, Bergler-Czop B, Stankowska A, et al. The safety of isotretinoin in patients with lupus nephritis: a comprehensive review. Cutan Ocul Toxicol 2016;1-8.
18. Siew ED, Matheny ME. Choice of Reference Serum Creatinine in Defining Acute Kidney Injury. Nephron 2015;131:107-12.
19. Akbari A, Clase CM, Acott P, et al. Canadian Society of Nephrology commentary on the KDIGO clinical practice guideline for CKD evaluation and management. Am J Kidney Dis 2015;65:177-205.
20. Yesilkaya B, Alli N, Artuz RF, et al. The frequency of hematuria in acne vulgaris patients during isotretinoin treatment. Cutan Ocul Toxicol 2016;1-3.
21. Demirseren DD, Kilinc F, Emre S, et al. The weeks and the cumulative doses of the first adverse events related to oral isotretinoin in acne patients: analysis of 300 patients. J Dermatol Treat 2016;1-5.
22. Morath C, Ratzlaff K, Dechow C, et al. Chronic low-dose isotretinoin treatment limits renal damage in subtotally nephrectomized rats. J Mol Med 2009;87:53-64.
23. Kiss E, Adams J, Grone HJ, et al. Isotretinoin ameliorates renal damage in experimental acute renal allograft rejection. Transplantation 2003;76:480-9.
24. Schaier M, Jocks T, Grone HJ, et al. Retinoid agonist isotretinoin ameliorates obstructive renal injury. J Urol 2003;170:1398-402.
25. Lehrke I, Schaier M, Schade K, et al. Retinoid receptor-specific agonists alleviate experimental glomerulonephritis. Am J Physiol Renal Physiol 2002;282:741-51.
26. Schaier M, Liebler S, Schade K, et al. Retinoic acid receptor alpha and retinoid X receptor specific agonists reduce renal injury in established chronic glomerulonephritis of the rat. J Mol Med 2004;82:116-25.
27. Adams J, Kiss E, Arroyo AB, et al. 13-cis retinoic acid inhibits development and progression of chronic allograft nephropathy. Am J Pathol 2005;167:285-98.
28. Witt O, Hammerling S, Stockklausner C, et al. 13-cis retinoic acid treatment of a patient with chemotherapy refractory nephroblastomatosis. J Pediatr Hematol Oncol 2009;31:296-9.
29. Kaymak Y. Creatine phosphokinase values during isotretinoin treatment for acne. Int J Dermatol 2008;47:398-401.
30. Landau M, Mesterman R, Ophir J, et al. Clinical significance of markedly elevated serum creatine kinase levels in patients with acne on isotretinoin. Acta Derm Venereol 2001;81:350-2.
31. Yildizgoren MT, Rifaioglu EN, Demirkapi M, et al. Isotretinoin treatment in patients with acne vulgaris: does it impact muscle strength, fatigue, and endurance? Cutis 2015;96:33-6.