ORIGINAL ARTICLE

Study of adverse effects of oral retinoids in Oman

Lutfi Al-Kathiri,[1] MD, Degambar Banodkar,[2] MD, Tasneem Al-Najjar,[3] MD

[1]Consultant Dermatologist and Head of Dermatology, [3]Medical Officer, Sultan Qaboos Hospital, Salalah, Oman
[2]Senior Consultant Dermatologist, EMC visitor, Oman

ABSTRACT

Background: Vitamin A and its derivatives (Retinoids) have been used successfully in dermatology for many years to treat several conditions such as psoriasis, pityriasis rubra pilaris, disorders of cornification and nodulocystic acne. As retinoids are potent teratogen, strict measures for pregnancy prevention during and after their use are implemented. Other side effects are generally preventable or manageable through proper patient selection, dose adjustments, and routine monitoring.

Objectives: This study aimed to report all dermatological and systemic side effects in all Omani patients received oral retinoids (isotretinoin in doses ranging from 0.5-1 mg/kg/day and acitretin in doses ranging from 0.25-1 mg/kg/day) from July 2010 to January 2012. It aimed also to determine common, serious, dose-related and any newer side effects of systemic retinoids and to compare them with those observed internationally.

Methods: This is a retrospective cross-sectional descriptive study, that included all Omani patients who received retinoid therapy between July 2010 and January 2012 in two centers in Oman; Al-Nahdha Hospital in Muscat and Sultan Qaboos Hospital (SQH) in Salalah. Details of patients' demographic information, dose, indication and duration of retinoids therapy as well as dermatological and systemic adverse effects were collected from medical records available in both hospitals. A questioner was filled for every patient. A single investigator was selected to conduct a direct personal interview with most of the patients to confirm the computer data.

Results: A total of 515 Omani patients received oral retinoids. The acute mucocutaneous toxicities; the most commonly observed side effects, were dose-dependent, typically well tolerated, readily treatable, and reversible. Cheilitis was the most commonly reported adverse effect, affecting 84.9% followed by cutaneous xerosis seen in 19.6% then dry eyes in 10.9% of patients. Other systemic toxicities reported include effects on the musculoskeletal, neurologic, gastrointestinal systems and laboratory abnormalities (e.g. hypertriglyceridemia, transaminitis and leukopenia) and all were reversible. The adverse effects that led to discontinuation of retinoids were pseudotumor cerebri and severe depression. There was no reported teratogenicity, bone toxicity or suicidal attempts in our study.

Conclusion: Retinoids are safe and effective therapy in many dermatological dermatoses. It should be used in lowest effective doses to help minimize side effects that may interfere with patient compliance. Retinoid-related adverse effects observed in Omani population are compatible with those observed internationally. As retinoids are potent teratogens, a strict requirement for pregnancy prevention during and after their use is essential. Proper patient selection, dose adjustments, close patient monitoring and patient education can minimize the occurrence of complications from retinoids.

INTRODUCTION

Retinoids are synthetic derivatives of vitamin A (retinol). Three generations of synthetic retinoids have been developed. They are different not only in their spectra of clinical efficacy but also in their toxicities and pharmacokinetics. First generation includes isotretinoin, members of second generation are etretinate and acetriten and third generation (also called arotinoids) include bexarotene, adapalene, and tazarotene. Oral retinoids are involved in the regulation of diverse biologic functions. They affect cellular growth, differentiation and morphogenesis, inhibit tumor promotion and malignant cell

Correspondence: *Dr. Lutfi Al-Kathiri, Consultant Dermatologist and Head of Dermatology, Sultan Qaboos Hospital, Salalah, Oman*

growth, exert immunomodulatory action, and alter cellular cohesiveness.[1]

The efficacy of systemic retinoids therapy in a number of dermatologic diseases are well established as a single most effective class of drug available for severe acne[2] and many disorders of cornification (e.g. ichthyosis), psoriasis vulgaris, pityriasis rubra pilaris and cutaneous T-cell lymphoma; however, concerns about potential side effects limit their use, especially in children.[3] Moreover, retinoids are potent teratogens, leading to strict requirements for pregnancy prevention during and after their use.[4] Other systemic toxicities include effects on the musculoskeletal, neurologic, gastrointestinal systems and laboratory abnormalities (e.g. hypertriglyceridemia, transaminitis). Concerns regarding serious systemic side effects are greater for those on high doses of oral retinoids for longer periods of time. Proper patient selection, dose adjustments, close patient monitoring and patient education can minimize the occurrence of complications.[2,5]

This study aimed to report all side effects in all Omani patients who received oral retinoids (isotretinoin 0.5-1 mg/kg/day and acitretin 0.25-1 mg/kg/day) in Al-Nahdha hospital & SQH from July 2010 to January 2012 as well as to determine common and serious side effects, age and gender distribution, doses related side effects and any newer side effects.

METHODS

This is a retrospective cross-sectional descriptive study conducted in AL-Nahda Hospital and SQH from July 2010 to January 2012. The targeted population consisted of 515 Omani patients who received oral retinoids (isotretinoin and acitretin).

Data were collected from the electronic health records available in both hospitals and a questionnaire was filled for every patient. It included patients' demographic information; age and sex, information regarding dose, indication and duration of retinoid therapy and dermatological and systemic side effects of retinoids. Laboratory blood tests of complete blood count (CBC), lipid profile and liver function tests (LFT) were reviewed in different stages of treatment; before starting retinoid therapy, one month after, and then every 2 months until completion of treatment.

A single investigator was selected to conduct a direct personal interview with most of the patients to confirm the computer data.

Written consents were taken from all patients receiving the treatment and the possible side effects were explained to them. Confidentiality was maintained. The study was approved by the Ethical Committee in Al-Nahdha hospital.

The data analysis was done by the statistical package for social sciences (SPSS) software system using descriptive statistics, cross-tab and graphs.

RESULTS

Age and gender distribution of patients on retinoids:

A total of 515 Omani patients who received retinoids were included in this study. The age of patients ranged from 5 to 80 years with mean age 27.8 years. The majority of patients (58.4%) were within the age interval of 20-29 years, while the lowest percentage of patients (0.97%) was within the age group (0-9) years. (See Fig. 1)

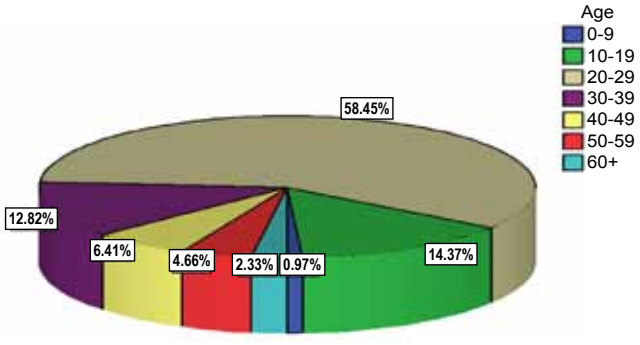

Fig. 1 Age distribution of patients on retinoids.

Our study included almost similar number of male and female patients. There were 45.05% (232) female patients and 54.95% (283) male patients. The ratio of males to females was approximately (1:1.2)

Indications of retinoids in Omani patients:

The most common indications of retinoid therapy in Omani population were nodulocystic acne which accounted for 361 cases, followed by psoriasis (97 cases), then ichthyosis; mainly lamellar type (12 cases). The rest of the indications are shown in fig. 2.

Adverse effects of retinoids:

The highest incidence of adverse events occurred in patients who received highest

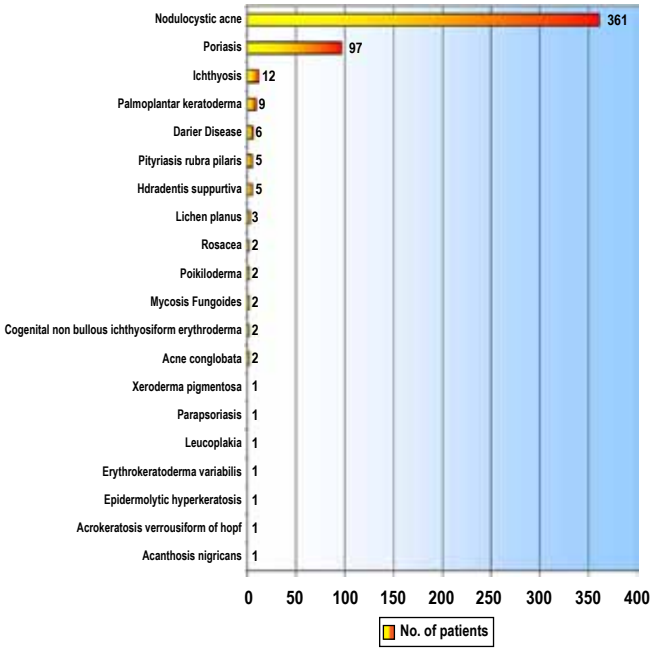

Fig. 2 Common indications of retinoids in Oman.

Table 1 Adverse effects frequently reported during retinoid clinical study

Side Effects	Patients No.	Percentage
Cheilitis	437	84.90%
Cutaneous xerosis	101	19.60%
Hypercholesterolemia	57	11.10%
Dry Eyes	56	10.90%
Leucopenia	55	10.70%
Decreased HDL	43	8.30%
Mild Headache	30	5.80%
Telogen Effluvium	29	5.60%
Hypertriglyceridemia	27	5.20%
Menstrual Irregularities	25	4.90%
Arthralgia	21	4.10%
Increased ALT	18	3.50%
Nausea	17	3.30%
Retinoid Dermatitis	15	2.90%
Epistaxis	15	2.90%
Exacerbation of acne	15	2.90%
Photosensitivity	11	2.10%
Palmoplantar& Digital desquamation	10	1.90%
Nasal Mucosa Dryness	10	1.90%
Fatigue	8	1.60%
Nail Fragility	7	1.40%
Mild depression	7	1.40%
Paronychia	6	1.20%
Myalgia	5	1.00%
Abdominal Pain	4	0.80%
Blepharoconjunctivitis	3	0.60%
Onychomycosis	3	0.60%
Dry Mouth	2	0.40%
Stickiness sensation (palm & soles)	2	0.40%
Cutaneous Staphylococcal aureus infections	2	0.40%
Decreased nasal mucous secretion	2	0.40%
Severe depression	2	0.40%
Sore Mouth & Tongue	1	0.20%
Photophobia	1	0.20%
Abnormal hair texture & dryness	1	0.20%
Diarrhea	1	0.20%
Pseudotumor cerebri	1	0.20%
Alopecia areata	1	0.20%

doses (>50 mg /day). Table 1 shows the adverse effects frequently reported during retinoid clinical study.

The dermatologic and systemic side effects were divided into 2 categories, minor and major side effects.

Relatively Common Minor Adverse Effects Due to Systemic Retinoids

Mucocutaneous Effects: In analysis of 515 patients receiving retinoids at standard recommended doses, cheilitis was the commonest encountered mucocutaneous effects which occurred in 437 patients (84.9%) (Fig. 3), followed by cutaneous xerosis in 101 patients (19.6%), dry eyes in 56 patients (10.9%), retinoid dermatitis in 15 patients (2.9%), photosensitivity in 11 patients (2.1%), palmoplantar desquamation in 10 patients (1.9%), nasal mucosal dryness in 10 patients (1.9%), blepharoconjunctivitis in 3 patients (0.6%), dry mouth, stickiness sensation (palms and soles) ,cutaneous Staph. aureus infections and decreased nasal mucous secretion; each was found in 2 patients (0.4%) and sore mouth and tongue and photophobia; each was found in 1 patient (0.2%).

Hair and Nails Effects: Hair changes during retinoid therapy including telogen effluvium were noted in 29 patients (5.6%), abnormal hair texture and dryness in one patient (0.2%) and alopecia areata in one patient (0.2%). Nail fragility was seen in 7 patients (1.4%), paronychia in 6 patients (1.2%) and onychomycosis in 3 patients (0.6%)

Musculoskeletal Effects: Arthralgias were noted in 21 patients (4.1%), fatigue in 8 patients (1.6%) and myalgia in 5 patients (1.0%).

Neurological Effects: These included mild headache which occurred in 30 patients (5.8%), and mild depression and mood changes seen in 7 patients (1.4%).

Gastrointestinal Effects: Nausea occurred in 17 patients (3.3%), abdominal pain in 4 patients (0.8%) and diarrhea in one patient (0.2%).

Potentially Serious Adverse Effects Due to Systemic Retinoids

Lipid Effects: Increased in total cholesterol (defined as > 5.2 mmol/L) occurred in 57 patients (11.1%), and increases in triglyceride levels (defined as > 1.7 mmol/L) occurred in 27 patients (5.2%). In addition levels of high density lipoprotein (HDL) decreased (defined as < 0.91 mmol/L) in 43 patients (8.3%). (Fig. 4). Comparison of levels of cholesterol

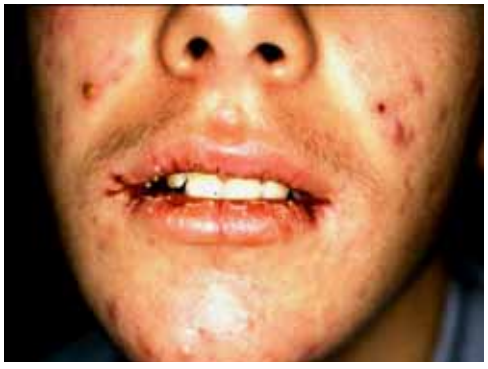

Fig. 3 Cheilitis.

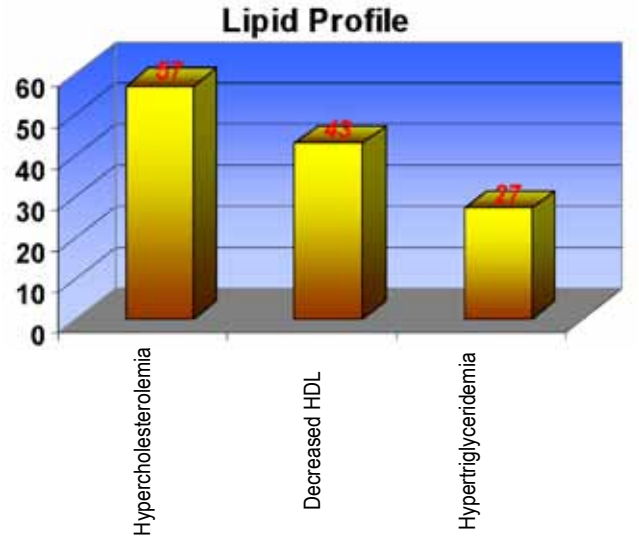

Fig. 4 Lipid effects during retinoid therapy.

during each lipid checkup in 57 patients with hypercholesterolemia showed that the average raise reached a maximum point of 5.59 mmol/L, and the average raise in triglyceride levels in 27 patients with hypertriglyceridemia reached a maximum point of 2.33 mmol/L. In addition the average drop of HDL levels reached a minimum point of 0.86 mmol/L in 43 patients with decreased HDL.

Liver Effects: Increased in Alanine aminotransferase (ALT); defined as > 40 IU/L, was seen in 18 patients (3.5% of patients), and average maximum elevation in ALT during regular follow up visits in patients with increased ALT was 58.92 IU/L

Hematologic effects: 55 patients (10.7%) on retinoid therapy had leucopenia (defined as < 4.00 K/UL) and the average levels during checkup visits showed lowest point at 3.55 K/UL.

Major neurologic Effects: Pseudotumor cerebri or benign intracranial hypertension occurred in 1 patient in our study (0.2%); this effect has not been associated with doxycycline or tetracycline administration. The patient was also complaining of visual changes and nausea. Retinoid treatment was then discontinued and the patient referred immediately to ophthalmologist where papilledema was confirmed.

We have reported two cases with severe depression on isotretinoin therapy (0.4% of patients). Retinoid discontinued immediately in both, and restarted in one of them after few months with lower dose and a good compliance.

Pancreatitis: Increased of serum triglyceride to levels associated with pancreatitis are uncommon, although one case of transient abdominal pain and acute pancreatitis occurred during the first week of retinoid treatment, the patient's triglyceride levels base line and subsequent checkup were within normal levels, so this elevation in pancreatic enzyme was either due to direct effect of retinoid on pancreas or accidental and not related to serum triglyceride. This patient improved after few days and isotretinoin was continued.

Teratogenicity: Teratogenicity was not reported in our study.

Hyperostosis: There was no radiography done as a routine investigation for our patients, and we have not encountered any patients having bone symptoms. Few patients receiving long term retinoids were screened for bony changes. However there were no abnormalities found.

Drug interaction: concurrent use of retinoids and other therapies that may increase the risk of side effects were not seen in this study.

Other Side Effects

Exacerbation of Acne: we have noticed exacerbation of acne lesions (Fig. 5), after starting Isotretinoin therapy for the first few weeks in 15 patients (2.9%), this effect has totally disappeared on continuation of treatment and by adding a short course of prednisolone in some cases.

Menstrual cycle Effects: We have reported 25 female patients (4.9%) having menstrual

Fig. 5 Flare up of acne.

irregularities in the form of delayed period and long term amenorrhea, which were reversible after discontinuation of retinoid therapy.

DISCUSSION

We have studied both the dermatological and systemic side effects induced by isotretinoin and acitretin. The frequency of mucocutaneous side effects was common, dose-dependent and compatible to that found in the literature. Cheilitis occurred in 84.9% (437) of cases and cutaneous xerosis and dryness of mucus membranes were reported in 32.4% (172), being similar to that showed in literatures in which cheilitis was reported in 87-100%, dry eyes in 19% to 87%, dry nose in 27% to 69% and dryness of the oral mucosa in 14% to 87%.[6,7,8,9] Photosensitivity was seen in 2.1% (11) patients in our study and as shown in the literature is noted particularly with isotretinoin which might be probably due to reduction of thickness of stratum corneum.[2] Etretinate and acitretin, in particular, have been shown to lead to palm, sole, and finger tips desquamation and increased skin fragility and was reported in 10 cases in our study.[6,7,8]

The initial report of ocular adverse effects was in 1979, describing isotretinoin-induced blepharoconjunctivitis, occurring in 20% to 50% of patients.[10] S. aureus colonization of conjunctival sac increases significantly during isotretinoin therapy.[11] However, bacterial conjunctivitis develops in only 7% of patients. The mechanism responsible for ocular adverse effects is believed to be decreased tear formation, as well as decreased lipid content in the tears.[10] Our study reported blepharoconjunctivitis in only 0.4% of patients. Our study reported blepharoconjunctivitis in only 0.6% of patients.

None of the effects mentioned were a reason to suspend the drugs. Symptoms were controlled with lip balm and body moisturizers, eye drops, ophthalmologic evaluation and orientation.

Isotretinoin has been shown to stimulate granulation tissue, which can occasionally lead to pyogenic granuloma-like eruptions that arise in sites of minor trauma and within acute lesions.[12] Similarly, periungual granulation tissue formation at sites of paronychia has been reported.[13] We have not encounter any case with pyogenic granuloma in our study.

Hair changes including telogen effluvium (the most common) were noticed in 5.6% (29) of our patients and were greater with acetriten compared to isotretinoin. Abnormal hair texture and dryness in 0.2% (1) and alopecia areata in 0.2% (1) of patients, nail fragility in 1.4% (7), paronychia in 1.2% (6) and onychomycosis in 0.6% (3) of patients. The risk of telogen effluvium due to the retinoids has been reported to vary over a range of 10% to 75%.[1,14,15] The risk is greater for acitretin than etretinate therapy, and is much less common for isotretinoin and bexarotene.[2] Hair loss is a dose-related reversible effect starting 2 months after either discontinuation of therapy or significant dose reduction. Women seem to have a more noticeable hair loss, particularly if there is already a mild baseline androgenic alopecia.[2]

Musculoskeletal adverse effects including mild arthralgia, fatigue and myalgia were seen in 34 cases (6.7%) during the first week of treatment. Reviewing the literatures showed that myalgia is noted in 15% of isotretinoin-

treated patients, particularly if they practice intense physical activity.[2] These muscle effects are associated mostly with isotretinoin therapy. Generalized increase of muscle tone due to etretinate and acitretin-induced myopathy has been reported.[16] The mechanism involved in adverse muscle effects is not known. High-risk patients are those whose professions or hobbies include heavy exertion.[2] Heudes and Laroche[17] reported unusually high rates of muscular complications in which 60% of patients had muscle symptoms; 51% had myalgia; and 41% had elevated creatinine phosphokinase (CPK) levels. In all, 5 patients had CPK levels 5 times normal value fulfilling diagnostic criteria for rhabdomyolysis. Landau et al[18] studied young adults with acne on isotretinoin and reported an incidence of markedly elevated CPK greater than 5000 IU/L in 1.58% of patients. Physical activity or intramuscular injection before blood testing was reported in 6 of 7; only 2 of 7 patients experienced concomitant myalgias. CPK values returned to normal within 2 weeks and the authors concluded that "hyperCPKemia" associated with isotretinoin therapy are a benign phenomenon. Furthermore, a high incidence of arthralgias and back pain in adolescents taking isotretinoin was observed in a recent study in 22% and 29% of patients respectively. Hull and Demkiw-Bartel[19] monitored adolescents and adults for side effects while on a 20-week course of isotretinoin for acne. They found 28.1% had back pain after the first month of therapy, 14.1% had myalgias, and 21.5% had arthralgias. The cause and significance of the back pain is unknown. In both these studies, there were no control groups, raising questions about the level of such symptoms.[20]

Few patients complained of mild neurologic side effects mainly with isotretinoin including headache and fatigue which can occur occasionally with isotretinoin therapy as shown in literaturs.[21] However, headaches associated with nausea, vomiting, and visual changes should prompt further evaluation to exclude pseudotumor cerebri. Lee[22] reported on a 14-year-old boy who had pseudotumor cerebri developed while on tetracycline and isotretinoin for acne; after 3 weeks of therapy, he presented with headaches and bilateral vision loss secondary to papilledema. Although combined therapy with isotretinoin and tetracycline, doxycycline, or minocycline increases the risk of pseudotumor cerebri, it can occur as a result of oral retinoid use alone. Roytman et al[23] described the case of a 16-year-old girl on isotretinoin (0.7 mg/ kg/d) for acne who experienced severe headaches and impaired night vision 2 months after the start of therapy. The symptoms abated when isotretinoin was discontinued and systemic corticosteroids were administered. There is a single case report of pseudotumor cerebri in an adult patient receiving acitretin without concomitant antibiotic use.[24] We have encountered 1 case of pseudotumor cerebri, however, neither tetracycline nor doxycycline were involved. Patient improved after cessation of therapy.

There were no reports of psychosis, suicidal attempts or irreversible hearing impairment in our patients. It has been reported that acne is associated with increased anxiety and depression, and decrease quality of life while treatment of acne with isotretinoin has been associated with improved quality of life, and reduced anxiety and depression.[25-29] Conversely,

depressive symptoms and depression have been reported in persons taking isotretinoin. Hazen et al[30] treated 110 patients for acne and disorders of keratinization with isotretinoin; 5.5% experienced depressive symptoms. In another study, depression was noted in 11% of 92 patients with acne treated with isotretinoin for 16 weeks.[31] In our study two cases with severe depression on isotretinoin were reported, and retinoid discontinued immediately, and restarted in one of them after few months for recalcitrant acne, with a lower dose with a good compliance.

Gastrointestinal effects including nausea, abdominal pain and diarrhea were experienced by few patients in our study and were mainly associated with isotretinoin. Nausea occurred in 3.3% (17), abdominal pain in 0.8% (4) and diarrhea in 0.20% (1) of patients. Reviewing the literatures showed that nonspecific gastrointestinal symptoms (nausea, diarrhea, abdominal pain) have been reported with isotretinoin therapy but are uncommon. A temporal relationship between isotretinoin therapy and inflammatory bowel-disease flares has been reported, but no cause-and-effect relationship has been established.[32,33] In fact, isotretinoin has been repeatedly administered to patients with known ulcerative colitis and crohn's disease without complications. In those rare cases in which inflammatory bowel disease flares during isotretinoin therapy, discontinuation of the drug is indicated.[34]

One patient in our study had abdominal pain and acute pancreatitis during the first week of isotretinoin therapy, this elevation in pancreatic enzymes was associated with normal level of triglyceride which could be direct effect of isotretinoin or coincidental increased in pancreatic enzymes. Pancreatic enzymes normalized after few days and patient continued isotretinoin therapy. Acute pancreatitis has been rarely encountered in patients taking first-or second-generation retinoids. Elevation of serum triglyceride to level associated with pancreatitis is uncommon. Two cases of acute pancreatitis with oral alitretinoin use and one case of fatal fulminant pancreatitis with acetriten treatment have been reported.[25,35] A high incidence of acute pancreatitis (1% to 3%) has been observed in patients treated with bexarotene >300 mg/m2/day and associated with marked elevations of fasting serum triglycerides.[7] The lowest triglyceride level that resulted in pancreatitis was 770 mg/dl; most patients experiencing pancreatitis had triglyceride levels well over 1000 mg/dl. Patients who have risk factors for pancreatitis (e.g., prior pancreatitis, uncontrolled hyperlipidemia, excessive alcohol consumption, elevated triglyceride levels associated with pancreatic toxicity) should avoid retinoid treatment.[2] All patients should be explained about the potential occurrence of pancreatitis and advised to promptly report any significant acute abdominal symptoms such as severe pain or emesis.[36]

Teratogenicity was not reported in our study due to strict measures undertaken. The female patients in child bearing period after signing consent and after confirmation of pregnancy test were strongly advised to use contraception 1 month before starting retinoid therapy and 1 month after treatment with isotretinoin and 3 years after treatment with acetriten.

Isotretinoin, etretinate, and acitretin are potent teratogens, and fetal deformities are the major

concern in treating fertile women with oral retinoids. The birth defects characteristically induced by retinoids, known as retinoic acid embryopathy, include central nervous system abnormalities (hydrocephalus, microcephaly), external ear abnormalities (anotia, small or absent external auditory canals), cardiovascular abnormalities (septal wall and aortic defects), facial dysmorphia, eye abnormalities (microphthalmia), thymus gland abnormalities, and bone abnormalities.[37,38] Additional reported defects include premature births, parathyroid hormone deficiency, and cases of low IQ in the absence of other central nervous system abnormalities.[39] The clinical expression of retinoic acid embryopathy may vary with the retinoid: etretinate is less likely to induce cardiac malformations and more likely to induce acral skeletal malformations.[40]

We have not encountered any patients having bone toxicity. Few patients receiving long term retinoids were screened for bony changes, however; there were no abnormalities found.

Subsequent prospective studies, have shown that retinoid effect on bone, if present at all, likely involve worsening of preexisting skeletal overgrowth rather than de novo changes, however, routine annual radiography is not warranted unless indicated by the presence of symptoms or long-term use of high dose of retinoid.

Adverse skeletal effects reported with oral retinoids closely resemble the bone findings of hypervitaminosis A.[41] Synthetic retinoids produce bony changes resembling diffuse idiopathic skeletal hyperostosis, including anterior spinal ligament calcification, osteophytes, and bony bridges, but without narrowing of the disk space. However, diffuse idiopathic skeletal hyperostosis is common in the general population who has never been treated with systemic retinoids. Jones et a[42] found that up to 65% of individuals younger than 20 years of age showed some degree of anterior osteophyte formation. In a skin cancer prevention study in patients with xeroderma pigmentosum, calcification of the anterior spinal ligament with bony bridging of vertebrae was observed after 2 years of high-dose isotretinoin therapy at 2 mg/kg/d.[43] Extraspinal tendon and ligament calcification was identified as a common toxicity in a study of 38 adult patients who received long-term (average: 5 years) etretinate therapy at an average dose of 0.8 mg/kg/d.[44] In children, ligamentous calcification secondary to oral retinoid use is very unusual.[45] Premature epiphyseal closure resulting in retardation of growth is a recognized manifestation of chronic vitamin-A intoxication, but has been rarely described in children receiving oral retinoid therapy.[46] Fibrodysplasia ossificans progressiva is a rare bone disorder of ectopic bone formation in muscles and other tissues. Zasloff et al[47] treated 21 children (ages 3-21 years) with high-dose isotretinoin (up to 8 mg/kg/d) for fibrodysplasia ossificans progressiva. By contrast, many authors have reported no significant osseous changes, and normal growth and development in children under chronic retinoid therapy.[48,49,50]

Other side effects observed in our study included menstrual cycle abnormalities that were seen in 4.9% (25) patients after starting retinoid and were reversible after cessation of therapy. Studies of retinoid effects on menstrual cycle are limited. From September

1982 to June 1987, 513 patients of the Group Health Cooperative of Puget Sound, Seattle, Wash, were prescribed isotretinoin for acne, and were observed throughout the first 4 to 5-month course of therapy for effectiveness and adverse effects where amenorrhea was seen in 2 patients.[51] In addition 2.9% (15) of patient experienced exacerbation of acne after initiating the treatment. This effect occurs temporarily and disappears on continuation of treatment and by adding a short course of prednisolone in some cases. Studies reported that flare of acne is common at the beginning of isotretinoin treatment; however, severe flare is rare. Multiple comedones, male gender and young age are reported as promoting factors.[52]

The analysis of laboratory exams showed a mild, nearly insignificant, elevation of serum ALT that occurred in 3.5% (18) patients; this elevation reached its maximum point in the first month of treatment and then decline in spite continuation of therapy.

Transaminase elevations greater than 3 times the upper normal range should lead to prompt retinoid discontinuation. With twofold to threefold transaminase elevations, therapy should be discontinued until the laboratory abnormalities return to normal. Subsequently, the retinoid therapy can possibly be resumed at a lower dosage, with very careful laboratory monitoring. With smaller enzyme elevations, the levels generally return to baseline while the patient is still receiving therapy without sequelae.[10,53]

Studies showed that elevated LFTs, most commonly the transaminases, can occur in approximately 15% of patients on oral retinoid therapy.[21] These are generally mild and return to normal within 2 to 4 weeks, despite continued therapy. In children with disorders of keratinization on acetriten, Lacour et al 54 reported an incidence of 14% of cases with transient liver enzyme alterations that did not require cessation of therapy. Significant hepatitis associated with isotretinoin or etretinate, although reported in adults, has never been reported in children.[21] Prospective studies have failed to demonstrate a causal relationship between long term retinoid therapy and chronic liver toxicity.[55] In fact, adult patients with Gilbert syndrome have had normalization of their hyperbilirubinemia while undergoing isotretinoin therapy.[56]

In our study increases in total cholesterol (defined as > 5.2 mmol/L) occurred in 11.1% (57), and increases in triglyceride levels (defined as > 1.7 mmol/L) occurred in 5.2% (27) of patients. In addition levels of HDL ("good cholesterol") decreased (defined as < 0.91 mmol/L) in approximately 8.3% (43) patients.

Base line serum lipid should be obtained before initiating retinoid treatment and 2-4 weeks thereafter until the effect on lipids is established. Lipid abnormalities may be managed by reducing the dose of retinoid, making appropriate dietary changes, or by means of lipid-lowering medications. Lipid level normalized in most of patients after discontinuation of retinoid therapy.

In clinical trials for isotretinoin, marked elevations of serum triglycerides in excess of 800 mg/dL were reported in approximately 25% of patients.[20] In addition, approximately 15% had a decrease in HDL and about 7% showed an increase in cholesterol levels. These effects were reversible on cessation of isotretinoin. Bershad

et al[57] found similar lipid profile trends, but less dramatic rises in triglycerides, in 60 otherwise healthy patients (ages 14-40 years old) treated with isotretinoin for 20 weeks. They observed that isotretinoin induced lipid abnormalities generally occurred early during therapy in men and at a much slower rate in women. Plasma lipid and lipoprotein levels returned to baseline by 8 weeks after discontinuation of the drug. Retinoid-induced hyperlipidemia is a dose-dependent phenomenon and is of particular concern in patients with obesity, high alcohol intake, diabetes, and pretreatment hypertriglyceridemia. This is typically not so much an issue in the average pediatric patient as it would be in an adult being considered for retinoid therapy. When triglyceride levels are very high (>1000 mg/dL), patients are at risk for xanthomata and acute pancreatitis.58 Lestringant et al[59] have suggested that the transient elevations in triglycerides and in the LDL/HDL ratio that occur during retinoid therapy have no meaningful effect on long-term cardiovascular health.

Our study also reported a hematological side effect; 10.7% (55) of our patients had leucopenia, and the level of WBCs declined from baseline to reach a steady level after 4 weeks of giving retinoid therapy. This effect was reversible after one month of cessation of therapy. However, in our patients the levels of leucopenia were acceptable as it has been generally observed that Omani people are having low WBCs count.[60] There were no complications reported due to leucopenia.

In CTCL studies, up to 43% of patients receiving bexarotene (>300 mg/m2/day) had reversible leucopenia (1000 to 3000 WBC/mm).[7,8] The onset of leucopenia typically ranges from 4 to 8 weeks. The leucopenia observed in most patients was dose-related and explained by neutropenia. There was no febrile neutropenia or serious infections. Leucopenia and neutropenia resolved after dose reduction or discontinuation within 30 days. The incidence of leucopenia and other hematologic abnormalities is much less frequent with first and second-generation retinoids.[53]

Concurrent use of retinoids and other therapies that might increase the risk of side effects were not seen in this study. Retinoids therapy has been associated with hepatotoxicity, increased intracranial pressure, alterations in glucose tolerance, and photosensitivity.[61] Concurrent use of retinoids with other therapies having similar side effects may increase the risk of these adverse events. Tetracycline (increased photosensitivity, pseudotumor cerebri), minocycline (pseudotumor cerebri), alcohol (increased conversion to etretinate, hepatotoxicity), and other retinoids or vitamin A supplements in excess of minimal daily requirements (hypervitaminosis) should be avoided. Other therapeutic agents that may interact with retinoids and should be monitored carefully include antidiabetic agents (alterations in blood glucose), corticosteroids (hyperlipidemia, pseudotumor cerebri), and methotrexate (increased methotrexate level, hepatotoxicity).[62] Unsupervised excessive exposures to sunlight or sun lamps should be avoided because of increased photosensitivity during retinoid therapy.

CONCLUSION

Retinoid has been established as a safe, effective

treatment in a number of dermatologic diseases as for severe acne, disorders of keratinization, psoriasis, pityriasis rubra pilaris and cutaneous T cell lymphoma. Retinoids should be used in lowest effective doses to help minimize side effects that may interfere with patient compliance.

This study documents the adverse effect profile of retinoids (isotretinoin and acitretin) in a 515 Omani patients over 3-years period (from 2010 to 2012). Most of the reported side effects were dose-dependent. The most common adverse effects seen were mucocutaneous side effects which can be managed easily by using emollients for dry skin and lips, avoidance of contact lenses and application of artificial tears for dry eyes. Other systemic side effects were mild and reversible. Few cases with serious side effects were reported. One is a case of pseudotumor cerebri not associated with tetracycline, doxycycline or minocycline administration which improved after discontinuation of isotretinoin, another case of acute abdomen associated with elevated pancreatic enzymes but with normal triglyceride level, this effect may be coincidental or may be a direct effect of isotretinoin. However pancreatic enzymes normalized after few days and patient continued isotretinoin therapy. Moreover we reported two cases with severe depression in which retinoid was discontinued immediately in both patients and restarted in one of them after few months for recalcitrant acne with lower dose and a good compliance. There were no reported cases of teratogenicity, bone toxicity or suicidal attempts. Laboratory abnormalities encountered in this study including transaminitis, hyperlipidemia and leucopenia were mild and do not necessitate cessation of treatment and all were reversible after completion of treatment.

Most adverse effects associated with retinoids are preventable or manageable through proper patient selection, dose adjustments, and routine monitoring for potential toxicity. The side effects observed in Omani population are compatible with those observed internationally. Laboratory tests especially CBC, LFT and fasting Lipid profile should be done before initiating the therapy and to be repeated one month after therapy, and further every two months, till the patient cease to take the therapy. In child bearing age, strict contraceptive measures especially dual contraception's are recommended before giving retinoids.

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