[LITERATURE REVIEW]

Updated Physician's Guide to the Off-label Uses of Oral Isotretinoin

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ABSTRACT

While oral isotretinoin is renowned for its ability to treat acne vulgaris, many of its off-label uses continue to go underappreciated. Since the last review on the unapproved indications of isotretinoin, relevant publications have surfaced with new recommendations. This article attempts to provide physicians with the latest information regarding successful and unsuccessful use of isotretinoin as an effective treatment for dermatological conditions, such as rosacea, psoriasis, pityriasis rubra pilaris, condyloma acuminatum, granuloma annulare, Darier's disease, systemic cutaneous lupus erythematosus, nonmelanoma skin cancer, and hidradenitis suppurativa. Variations in dosage regimens and isotretinoin viability as an alternative to other standard treatments are also discussed in relation to these conditions.
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Since its United States Food and Drug Administration (FDA) approval in 1982, isotretinoin (13-cis-retinoic acid) has dramatically affected the field of dermatology.[1] Specifically, it has revolutionized the treatment of severe nodular-cystic acne, remarkably providing a cure for the condition.[2] However, what might be less known is that isotretinoin's powerful anti-inflammatory, immunomodulatory, antineoplastic, and other pharmacological properties have led to its "off-label" implementation in more than 50 non-acne dermatological conditions. As its implementation continues to expand, it is imperative to ensure that it is used properly. Some "off-label" implementations have been shown to be successful in well-documented studies while others continue to be used even though new publications have shown isotretinoin to be ineffective. This review focuses on providing the most updated information to allow clinicians to make informed, evidence-based decisions about whether isotretinoin could be used and how it should be implemented in some of the more complex dermatological conditions.

ROSACEA

Oral isotretinoin is one of few therapies able to effectively treat several subtypes of rosacea.[3–5] It appears to be most effective in treating papulopustular rosacea (PPR), though it has also demonstrated positive effects in both erythematotelangiectatic rosacea (ETR) and phymatous rosacea.[6–7] This has been attributed to isotretinioin's ability to reduce cutaneous blood flow and to decrease the size and number of sebaceous glands in the prefibrotic stages, respectively.[3,7–9] Its documented success in treating the common subtypes as well as severe and rare cases of rosacea makes isotretinoin a valuable treatment option.[10,11]

Variations in dosages available in literature. The standard isotretinoin dose for rosacea has formerly been between 0.5 and 1.0mg/kg daily.[12–14] It is now thought that this dose ineffectively treats rosacea, as the incidence of side effects increases and replaces rosacea-linked erythema with drug-induced facial dermatitis and xerosis.[15–16] These issues associated with the standard dose led to a number of studies exploring alternative reduced dose regimens. Two early publications demonstrated that 10mg daily of isotretinoin could effectively treat recalcitrant cases of rosacea, as it was shown to reduce erythema, telangiectasias, and papulopustular lesions.[4,6] A continuous "microdose" (mean of 34.2mg/week for up to 33 months) model was also shown to be effective in controlling flare-ups.[17] However, only recently has evidence been presented clearly establishing the most efficacious dose.

In hopes of achieving quicker response times, Uslu et al[18] recently implemented an "intermediate" 20mg/day dose in a 10-month trial. The introductory dose of 20mg/day was given for four months and then slowly tapered over the next six months to an end dose of just 20mg/week. Patients

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achieved significant improvements within the first month of therapy as demonstrated by decreased erythema (P=0.002) and sebum levels (P=0.000). This response time was much quicker than was previously achieved with other low-dose trials of 10mg/day, which reported improvements between Week 9 and 16.[4,6] Uslu et al concluded that 20mg/day was "rapidly efficient for reducing both inflammatory lesions and erythema in rosacea."

In 2009, Gollnick et al[16] also published favorable results with isotretinoin, reporting a 90-percent reduction in inflammatory lesions using a dose of 0.3mg/kg/day in a large, (N=573) 12-week, double-blind comparison study against doxycycline. The study concluded that 0.3mg/kg/day was significantly noninferior to doxycycline, which achieved an 83-percent reduction in lesions. The study also demonstrated that the 0.3mg/kg/day dose exhibited less dermatitis facialis than 0.5mg/kg, was more effective than 0.1mg/kg, and concluded that it should be considered a safe and effective alternative to doxycycline in PPR and phymatous rosacea.

According to this new data and previously published studies, it appears that oral isotretinoin is effective in treating refractory PPR and may also have a positive effect with other subtypes including ETR and phymatous rosacea.[19] The most efficacious dose is 20mg/day or 0.3mg/kg/day for a period of 6 to 10 months, which can be tapered after month four.[16,18] In addition, a continuous "microdose" might be considered to avoid relapse.[17]

Rare forms of rosacea. *Rosacea fulminans (pyoderma faciale).* Pyoderma faciale or rosacea fulminans, the latter name suggested by Plewig et al,[20] is a rare and severe form of rosacea that almost exclusively occurs in women.[10] As demonstrated by Rosen et al,[21] oral isotretinoin should be considered primary therapy as it is the only treatment modality that has shown consistent successful results.[21] Suggested treatment regimens often include a brief course of prednisone (40–60mg/day for 1–2 weeks with taper) to reduce inflammation, followed by a slow introduction of isotretinoin (0.2–0.5mg/kg/day then increased to 0.5mg/kg/day–1mg/kg/day). Isotretinoin should be continued for 3 to 4 months, until lesions have resolved or until a cumulative dose of 150mg/kg is achieved.[10,21–25]

Extrafacial rosacea. Although difficult to diagnose due to its atypical presentation and low index of suspicion, extrafacial rosacea (EFR) has been reported in multiple cases in the literature.[11,26–28] EFR predominantly affects men and is usually found in sun-exposed areas. It has responded favorably to isotretinoin via monotherapy and in combination with azithromycin and oral corticosteroids. Suggested therapies include isotretinoin at 10 to 20mg/kg/day or in combination with oral steroids (deflazacort 30mg for 3 weeks) and azithromycin (500mg, 3 days/week for 4 weeks).[11,26]

Other rosacea subtypes not specifically addressed here, but in which isotretinoin has been shown to be effective, include granulomatous rosacea and gram-negative rosacea.[29,30]

OTHER NON-ACNE DERMATOLOGICAL CONDITIONS TREATED WITH ISOTRETINOIN

Pityriasis rubra pilaris. Early diagnosis and treatment appear to be key in effective treatment and management of pityriasis rubra pilaris (PRP).[31] According to various authors, isotretinoin could be considered first-line therapy for PRP as it has demonstrated superiority over other treatment modalities including ultraviolet B (UVB)+tar, topical steriods, calcipotriene, keratolytics, methotrexate, azathioprine, high-dose vitamin A, and cyclosporine.[31,32] However, PRP continues to be a very challenging condition to treat and results with isotretinoin, as with other treatment modalities, are also often unsatisfactory.[33] Early success with isotretinoin includes a multicenter study demonstrating significant improvements in 43 of 45 patients with high-dose isotretinoin (2.13mg/kg/day),[34] 3 of 5 patients achieving a good clinical response to 2.0mg/kg/day (Peck et al, as cited in Akyol[2]) and Risch et al reported 3 of 5 patients achieving complete clearing with six months of therapy. (Risch et al, as cited in Akyol[2]). Others have also been successful with lower dose regimens. Dicken's[35] 4 of 5 patients were clear or mostly clear on 1mg/kg to 1.5mg/kg/daily. Likewise, Allsion et al's[32] implementation of 20mg/day for children and 40mg/day for adults was demonstrated to be effective. In yet another small case study, a 0.5mg/kg/day trial dose resulted in 50-percent improvement of 3 of 4 patients with one achieving complete clearing.[36] Treatment durations averaged 16 to 24 weeks with a typical response noticed by weeks 14 to 16.[2,31] With these long response times, it is very important to include a multimodality treatment approach emphasizing careful skin care with potent moisturizers and perhaps tap water dressings.[2] Also, in cases that evolve to become erythrodermic, prednisone (40mg/day) and brief hospitalization should be considered.[37]

PSORIASIS

Systemic retinoids address many pathological features of psoriasis including modulating inflammatory cells, keratinocyte hyperproliferation, and differentiation.[38] Some studies suggest that isotretinoin is ineffective in treating certain types of psoriasis, particularly plaque-type psoriasis. In fact, in early head-to-head studies, etretinate was found to be superior to isotretinion in treating most forms of psoriasis.[39,40] However, with a lengthy teratogenic half-life of 120 days and reports demonstrating its presence in serum up to two years post-therapy, etretinate was removed from the market in 1997. Its successor acitretin became the only systemic retinoid with a psoriasis-approved indication.[41]

Although the notable success of acitretin has made it favorable, it has been suggested that effective contraceptives be used 2 to 3 years post-acitretin and alcohol avoidance be implemented during treatment and two months post-therapy. This is due to *in vivo* studies that have demonstrated transesterification conversion of acitretin to etretinate with co-administration of alcohol.[42] In psoriasis cases affecting women of childbearing potential who wish to avoid long-term post-therapy contraceptive use, isotretinoin should be considered as a therapeutic option in view of its

significantly shorter half-life.

Isotretinoin has been shown to manage pustular-type psoriasis with dosages ranging from 40mg/day for children to 1.5 to 2.0mg/kg/day for adults with success rates exceeding 90 percent.[43] (Sofen et al as cited in Halverstam et al[44]). Perhaps of more therapeutic benefit however, are its recently demonstrated synergistic effects when used with either psoralen + ultraviolet A (PUVA) or narrowband ultraviolet B (NBUVB). In a recent 2011 randomized controlled trial involving 38 patients with plaque-type psoriasis, Mortazavi et al[45] demonstrated that the addition of 0.5mg/kg/day of isotretinoin in combination with NBUVB could significantly reduce the number of phototherapy sessions (30.29+/-9.17 vs. 38.15+/-3.39 (P=0.008)) and cumulative NBUVB dose (29.95+/-16.11J/cm^2 vs. 45.77+/-7.72J/cm^2 (p=0.004)) more than NBUVB used alone. They concluded that isotretinoin at 0.5mg/kg/day can be considered an effective alternative to acitretin in NBUVB combination therapy. Earlier published studies demonstrate similarly positive results involving combination therapy with PUVA, concluding that both isotretinoin-PUVA and PUVA-etretinate were superior to PUVA-placebo therapy.[39,46]

CUTANEOUS LUPUS ERYTHEMATOSUS

In a review of current literature, it appears that isotretinoin and acitretin are effective options for refractory cases of subacute cutaneous lupus erythematosus (SCLE), discoid lupus erythematosus (DLE), and chronic cutaneous lupus erythematosus (CCLE) and display similar efficacy as other common treatment modalities, including hydroxychloroquine.[47–54] One successful study involved a 16-week trial of isotretinoin (0.15mg/kg/day increased to 0.5mg/kg/day), which achieved clearing or clinical improvement with accompanying histopathological changes in 86.9 percent of the 24 patients involved (CCLE n=19 or SCLE n=5).[48] Scornick et al's[49] six patients with CCLE responded rapidly to 1mg/kg/day of isotretinoin, although recurrence of the condition occurred soon after discontinuation of therapy. Recently, a 26-year-old woman with refractory cutaneous lupus erythamatosous who had previously failed a long list of conventional therapies including extensive trials of prednisone, hydroxychloroquine, quinacrine, azathrioprine, and topical therapies, achieved remarkable improvement with one month of 40mg/day of isotretinoin.[47]

The drawbacks to systemic retinoid use in cutaneous lupus, apart from their known adverse side effects, appear to include the following: 1) a higher and more rapid recurrence rate upon discontinuation of therapy than seen with other commonly used systemic agents such as methotrexate. In cases of recurrence, implementation of a low maintenance dose might be a consideration as shown effective by Furner (Furner as cited in Richardson et al[50]); 2) there is a relative contradiction in cutaneous lupus associated Sjogren's syndrome due to pre-existing keratoconjunctivitis sicca; and 3) expense. Isotretinoin and acitretin are both significantly more expensive than methotrexate, hydroxychloroquine, and prednisone. Nevertheless, retinoid therapy can be implemented when needed, with the most accepted treatment regimen of isotretinoin being between 0.2 and 1mg/kg/day with a rapid response typically seen between 2 to 6 weeks.[47–50]

HIDRADENITIS SUPPURATIVA

Hidradenitis suppurativa (HS) is a distressing chronic inflammatory disorder characterized by persistent abscesses, sinus tract infections, and frequent scarring. The pathogenesis is thought to be associated with follicular occlusion and secondary apocrine gland dysfunction.[55] Multiple therapies have been attempted to treat HS with limited success. Its remote similarities to acne vulgaris has lead some clinicians to implement isotretinoin. Unfortunately, the results have been somewhat disappointing.[56–58] Success has been reported in small case studies, although most sources have found isotretinoin ineffective in controlling this condition.[2,56,59,60] Two available retrospective studies support this assumption. Boer and Van Gemert[57] reviewed 68 patients who had received isotretinoin (0.5–0.8mg/kg/day for 4–6 months) and recorded that 16 (24%) achieved complete clearing of disease and 25 (37%) showed lesser improvement. Almost all those who improved had mild HS involvement. This suggests that patients with more significant HS involvement are even less likely to respond to isotretinoin. In a recent and larger retrospective investigation, Sorria et al[61] investigated 358 patients with HS, 88 of whom were treated with isotretinoin between the years of 1999 and 2006. The mean treatment period was 7.8 months with an average dose of 44mg/day (20–140mg/day). They reported 14 (16%) patients with declared improvement, 67 (77%) with no improvement, and 6 (7%) patients whose condition worsened. Interestingly, while isotretinoin has had very limited success with HS, a recent publication by Boer et al[62] demonstrated promising results with acitretin.

GENERALIZED GRANULOMA ANNULARE

Generalized granuloma annulare (GA) is a noninfectious skin disorder characterized by widespread areas of annular papules, plaques, and occasionally nodules. Treatment attempts are often ineffective and the condition rarely resolves spontaneously, resulting in embarrassing and unsightly lesions.[63] The lack of established or consistent treatment approaches has promoted multiple case studies published on various treatment modalities, including the use of isotretinoin. While there is an absence of randomized controlled trials and large case studies on the treatment of generalized GA with isotretinoin, there are many individual case studies demonstrating good cosmetic results. The most common treatment approach includes implementing an isotretinoin dose of 0.5mg/kg/day with successful cases demonstrating near complete clearing within 2 to 6 months and with remission rates exceeding six months to one-year post-therapy.[64–69] If a partial response is achieved, increasing the dose to 1mg/kg/day might be considered as this dose has been shown effective in a few cases.[70,71] There are also multiple reports of relapse after discontinuation, and in such

cases a low maintenance dose for an additional three months to one year has been suggested.[66,72,73]

CONDYLOMATA ACUMINATA (ANOGENITAL WARTS)

As traditional treatment modalities for condylomata acuminata (CA) often produce unsatisfactory results, clinicians have implemented oral isotretinoin in hopes that its immunomodulatory properties might aid in the treatment of this condition.[2] It has been utilized in two forms: monotherapy and in combination with interferon alpha (INF-α). The available studies suggest that combination therapy may be a reasonable option in cases of recalcitrant CA. An effective treatment approach might include isotretinoin at a dose between 0.5 to 1mg/kg/day for up to three months with INF-α. The two commonly accepted INF-α dosage regimens are either daily intramuscular injections (IM) for three weeks ($3x10^6$U) or subcutaneous injections ($3x10^6$U) three times per week for four weeks.[74–76]

Two of three published studies regarding isotretinoin monotherapy have shown promising results. Georgala et al[77] reported 32.1 percent (9 of 28) of the women treated achieved complete clearing on 0.5mg/kg/day and Tsambaos et al[78] demonstrated a 37.5 percent (21 of 56) complete clearing rate in men on 1mg/kg/day. Meanwhile, Olsen et al[79] found no objective response in the seven patients treated with 1mg/kg/day of isotretinoin (p=0.009).

In combination therapy, Cardamakis et al[75] published the most conclusive data, demonstrating that the combination of isotretinoin (1mg/kg/day) plus interferon alfa-2a ($3x10^5$U SQ three times weekly) had a lower recurrence rate (4 of 44 vs. 16 of 42; P<0.01) and a shorter treatment interval (2.18 vs. 2.5 months; P<0.01) than did isotretinoin monotherapy. A more recent case study demonstrated that lower dosages of isotretinoin (0.5mg/kg/day) with interferon-alfa-2a can also be an effective treatment modality.[80] Yet in another comparison study involving women, Cardamakis et al[81] reported no difference in remission rates between combination INF-α/isotretinoin and montherapy (84.8% vs. 75%, respectively). However, the duration of treatment was significantly reduced in the combination therapy group (1.9 vs. 2.5 months, respectively p<0.01).

Additionally, it has been shown that INF-α is most successfully implemented as an adjunctive agent with either surgical excision, 5-fluorouracil creams, or laser ablation where it has demonstrated decreased recurrence rates, though this approach is still rarely used in clinical practice.[82] There are currently no studies exploring the possibility of using the isotretinoin/INF-α combination adjunctive therapy following traditional localized therapies, though this may be an approach to be explored more in the future.

DARIER'S DISEASE (KERATOSIS FOLLICULARIS; DARIER-WHITE DISEASE)

Darier's disease (DAR) is a genetic disorder that usually manifests before the age of 30. It is characterized by the presence of widespread areas of persistent crusted papules and hyperkeratotic plaques.[83] If symptoms are particularly severe, a trial of isotretinoin could be considered. There are currently no randomized controlled trials published on isotretinoin use in DAR, but several case studies have demonstrated its effectiveness.[84–88] In order to avoid long-term toxicity, a lower dose (0.2mg/kg/day) should be administered initially and then increased. The most efficacious dose is typically found between 0.5 and 1.0mg/kg/day. Symptomatic improvement is often reported within 2 to 4 weeks of therapy. Due to the chronic nature of this disorder, a continual low maintenance dose has also been implemented.[83] Ling et al[89] demonstrated that long-term use of isotretinoin with cumulative doses of up to 1075mg/kg did not cause significant radiological abnormalities. However, vigilance is required to avoid complications of long-term isotretinoin use including possible liver toxicity, hypertriglycidemia, and extreme teratogenic side effects avoidable through pregnancy prevention.

ISOTRETINOIN'S USE IN SKIN CANCER

The use of retinoids in chemoprevention and suppression is widely recognized. Isotretinoin, as with other retinoids, has been shown to induce cell differentiation, modulate growth, and induce apoptosis.[90–92] The exact mechanism is still not fully understood; however, it appears that many premalignant dysplastic lesions express low levels of nuclear retinoid receptor beta (RAR beta), which can be restored to near normal levels with retinoid therapy. This helps establish normal growth and differential of epithelial cells in the premalignant proliferating colonies.[93] In addition, retinoids also demonstrate antiangiogenic properties that may contribute to their antineoplastic activity.[94–96] These properties have led to the implementation of retinoids in prevention and treatment of precancerous conditions, such as leukoplakia and actinic keratosis (AK), and in more serious disorders, such as cutaneous T-cell lymphoma (CTCL), acute promyelocytic leukemia, head and neck cancer, nonmelanoma skin cancer (NMSC), hepatocellular carcinoma, breast cancer, and neuroblastoma.[97] This review discusses oral isotretinoin's specific use in select implementations related to dermatological conditions.

Precancerous dermatological implementations of isotretinoin. *Isotretinoin synergistic effects with topical fluorouracil.* Topical fluorouracil (5-FU) is currently approved for the treatment of AKs and is also often implemented for squamous cell carcinoma (SCC) *in situ*, "off-label". This approach is utilized in cases where other treatment modalities are impractical. In such cases, there is evidence of a synergistic effect when oral isotretinoin is used in combination with topical fluorouracil. Sander et al[98] noted that 5-FU/isotretinoin (20mg/day) combination therapy could drastically reduce the number of existing AKs, prevent the appearance of new lesions, and rapidly repair photodamaged skin more than 5-FU monotherapy. A recent *in vitro* study supports this assumption, determining that the combination of 5-FU and 13-cis retinoic acid increased cell apoptosis and inhibition of oral SCC cell line proliferation, significantly more than when either was introduced separately.[99] In this study, it was also noted that the addition of vitamin D_3 could further increase

TABLE 1. Oral isotretinoin: Reports on off-label uses

REFERENCED ARTICLE(S)	DERMATOLOGICAL CONDITION	NUMBER OF PATIENTS INVOLVED IN THE STUDY	TREATMENT REGIMEN	ADDITIONAL INFORMATION	CONCLUSION
Uslu et al[18]	Rosacea	25	20mg/day for 4 months	Dose was reduced to 20mg/week by 8 months	Rapidly efficient for reducing both inflammatory lesions and erythema in rosacea
Gollnick et al[16]	Rosacea	573	0.3mg/kg/day	The 0.3mg/kg/day dose was shown to be more efficacious than both the 0.1 and 0.5mg/kg/day	Effective and well-tolerated treatment option for rosacea subtypes II&III and successful alternative to doxycycline
11, 26	Extrafacial rosacea	1–8	10–20mg/day	Also used in combination with azithromycin and an oral glucocorticoid[26]	Marked improvement or complete resolution
10, 21–25	Rosacea fulminans	1	0.5–1mg/kg/day for 3–4 months, until lesions have resolved, or a cumulative dose of 150mg/kg	Begin with 1–2 weeks of prednisone followed by slow introduction of isotretinoin	Only treatment modality that has consistently produced a remission
Mortazavi et al[45]	Psoriasis	38	0.5mg/kg/day + narrowband ultraviolet B		Reduced the number of phototherapy sessions and accumulative dose
Cardamakis et al[75]	Condyloma accuminata	86	0.5–1mg/kg/day + INFα-2a ($3x10^5$ U subcutaneously) given 3 times/week		Higher remission rates and shorter treatment duration than isotretinoin alone
Vena et al[48]	Subacute cutaneous lupus erythematosus	24	0.5–1mg/kg/day	Higher recurrence rates upon discontinuation than with methotrexate	Clearing or complete resolution in 86% of patients
Sorria et al[61]	Hidradenitis suppurativa	88	Average of 44mg/day for 4–8 months		Only 14 of 88 (~16%) patients noted improvements
64–73	Generalized granuloma annulare	1	0.5–1mg/kg/day	Remission rates exceeding 6 months-1 year post therapy	Near complete clearing appreciated by about 2–6 months
84–88	Darrier's disease	1	0.5–1mg/kg/day for approximately 4 weeks		Responses noted by 2–4 weeks of therapy

apoptosis, which coincides with previously documented clinical studies.[100,101] This therapeutic approach is beneficial in patients with severe actinic damage, which is unlikely to respond to only one treatment of 5-FU. It is apparent that the addition of isotretinoin could possibly increase xerosis and irritation, adding discomfort to an already uncomfortable treatment method. However, Sander et al[98] noted that with low-dose isotretinoin, most xerosis and adverse mucocutaneous effects can be minimized.

Tables 1 to 3 summarize the results of recent studies involving the off-label implementations of oral isotretinoin in various dermatological conditions (a number of rare conditions and implementations not discussed in the text, yet worthy of note, are included and referenced as well).

TABLE 2. Oral isotretinoin: Use in chemoprevention and treatment

REFERENCED ARTICLE(S)	DERMATOLOGICAL CONDITION	NUMBER OF PATIENTS INVOLVED IN THE STUDY	TREATMENT REGIMEN	ADDITIONAL INFORMATION	CONCLUSION
Sander et al[98]	Actinic keratosis	27	20 mg/day for 3 weeks + topical fluorouracil		Synergistic effect noted
Lippman et al[103]	Leukoplakia	70	Induction dose of 1–1.5mg/kg/day for 3 weeks followed by a maintenance dose of 0.5mg/kg/day		55% of patients responded to induction therapy and 92% remained relapse free at 9 months
Kraemer et al[115]	Xeroderma pigmentosum	12	2mg/kg/day	Continual usage required to see a therapeutic benefit	63% drop in skin cancerous lesions observed over the course of the 3-year study
Duvic et al[106]	Cutaneous T-cell lymphoma	28	Combination therapy included 1mg/kg/day of isotretinoin +INFα at mean dose of $5x10^6$ IU/m^2/day SQ	In patients with stage 3 & 4, chemotherapy proceeded isotretinoin + INFα therapy	82% of patients experienced a complete or partial response. Stage 1 & 2 patients were relapse-free at 18 months post-therapy
Levin et al[121]	Nonmelanoma skin cancer in high-risk groups	525	5–10mg/day for 3 years		No significant decrease in appearance of tumors noted with daily isotretinoin use vs. placebo
Shin et al[110]	Advanced squamous cell carcinoma	66	1mg/kg/day for 38 months +IFNα ($5x10^6$ IU/m^2) for 3 weeks + cisplatin 20mg/m^2 for 1 week		No significant decrease in appearance of new or recurrent tumors
Brewster et al[127]	Squamous cell carcinoma in high-risk groups	66	1mg/kg/day + INFα ($3x10^6$ U SQ) 3 times a week	Higher recurrence rates upon discontinuation than with methotrexate	No significant decrease in appearance

LEUKOPLAKIA

There have been a few encouraging studies involving isotretinoin's use in leukoplakia. In one comparative study, Hong et al[102] reported that 16 of 24 (67%) patients achieved clinical improvements after three months of isotretinoin (1–2mg/kg/day) use. However, many patients experienced significant toxicity and 47 percent required a dose reduction. Further, more than half of the patients relapsed within three months. Due to high relapse rates, another study was conducted. This time, 70 patients underwent a trial of induction therapy (1.5mg/kg/day for three months) followed by a low maintenance dose of isotretinoin (0.5mg/kg/day for 9 months) versus beta-carotene (30mg/day). During the induction phase, 36 (55%) of the patients responded effectively. In the low-dose maintenance phase, isotretinoin achieved higher relapse free percentages (92% vs. 45%) than beta-carotene.[103] In hopes of reducing systemic effects, topical isotretinoin (0.18%) has also been successfully implemented.[104] Even so, others still remain critical of retinoid therapy in leukoplakia. As one recent article stated, "…despite good short-time effectiveness, retinoids do not prevent recurrences of the lesions and insignificantly increase cancer-free survival."[105]

ISOTRETINOIN'S USE IN TREATING CUTANEOUS CANCER

Currently, bexarotene (Targretin, Medicis, a division of Valeant Pharmaceuticals) is the only oral retinoid with FDA approval for treating advanced CTLC. However, isotretinoin and acitretin have also been successfully utilized. They are most often implemented in combination therapy with a variety of agents including chemotherapy, total skin electron beam (TSBE), PUVA, and INF-α.[2,106] In patients with CTCL (stages I–IV), Duvic et al[106] used INF-α/isotretinoin therapy

TABLE 3. Oral isotretinoin: Less commonly reported uses (continued on next page)

REFERENCED ARTICLE(S)	DERMATOLOGICAL CONDITION	NUMBER OF PATIENTS INVOLVED IN THE STUDY	TREATMENT REGIMEN	ADDITIONAL (INFORMATION	CONCLUSION	ADDITIONAL REFERENCES
Hartman et al[128]	Porokeratosis plantaris, palmaris, et disseminate	1	60–80mg/day	Frequent relapse observed with discontinuation	Marked reduction in number of lesions	
Gutierrez et al[129]	Facial porokeratosis	6			Moderate improvement seen in 2 of 6 patients	
130–136	Dissecting cellulitis	1–2	Commonly used in combination therapy at 1mg/kg/day for at least 4 months and then a maintenance dose of 0.75–1mg/kg/day		Execllent responses observed	
Helfman et al[137]	Grover's disease	4		High relapse rate upon discontinuation	3 of 4 patients responded with up to 10 months of remission	138
Multizwa et al[139]	Fordyce spots	2	1mg/kg/day	2 of 3 patients relapsed at 1 month of discontinuation	Rapid and effective response noted with in 2 weeks of therapy	140
Grimalt et al[141]	Sebaceous hyperplasia	1	20–40mg 3–4 times a week with maintenance of 40 mg twice weekly or topical isotretinoin	Improvements noted as early as Week 1	Improvements observed	142–146
Saleh et al[147]	Kyrle's disease	1			Complete clearing observed by 13 weeks	
Serdar et al[148]	Scleromyxedema	1	60mg/day for 6 months		Significant improvement	149–151
Layton et al[152]	Ulerythema ophryogenes	1			Positive response noted	
Berbis et al[153]	Ofuji's disease	1	1mg/kg/day and a 0.5mg/kg/day maintenance dose	Quick relapse noted after discontinuation	Dramatic improvement observed by Week 2 of treatment	

in combination with other treatment modalities and achieved an 82-percent response rate (complete or partial) and remission rates exceeding 18 months in patients with stage I and II CTCL. Similar success has also been demonstrated with acitretin.[107] The suggested dose is typically 1mg/kg/day for isotretinoin or 25 to 50mg/day of acitretin.[106–109]

Isotretinoin/INF-α combination therapy has also proved promising in the treatment of advanced SCC skin cancer, achieving success rates between 17 and 68 percent.[110,111] In a Phase 2 trial of 39 patients, Shin et al[110] reported overall and complete response rates of 34 and 17 percent, respectively, in advanced SCC using a combination of INF-α, 13-cis retinoic acid, and cisplatin. Lippman et al[111] reported similar success with INF-α/13-cis retinoic acid combination therapy. Out of 28 patients with advanced SCC, 19 (68%) responded to combination therapy and seven (25%) noted a complete response. A recent small case study also reported that isotretinoin (1mg/kg daily) in combination with daily radiotherapy, resulted in a rapid reduction in tumor size in

TABLE 3 continued. Oral isotretinoin: Less commonly reported uses

REFERENCED ARTICLE (S)	DERMATOLOGICAL CONDITION	NUMBER OF PATIENTS INVOLVED IN THE STUDY	TREATMENT REGIMEN	ADDITIONAL INFORMATION	CONCLUSION	ADDITIONAL REFERENCES
154–157	Steatocystomas	1	1mg/kg/day	Worsening of condition with isotretinoin use has been reported	Improvements noted	
158–159	Diffuse dermal angiomatosis of the breast	1	40mg/day		Lesions improved	
160–161	Pachydermoperiostosis	1			Dramatic improvements observed by Week 4	
Apalla et al[162]	Atrophoderma vermiculatum	1	0.5mg/kg/day for 2 separate 6-month periods		Improved cosmetic appearance	
Richard et al[163]	Keratosis follicularis spinulosa decalvans	1	0.5mg/kg/day for 12 weeks		Persistent lesions, but with noted improvement	
Graefe et al[164]	Muir-Torre syndrome	1	50mg/day + INFα-2a ($3x10^6$ U SQ) 3 times a week + topical isotretinoin		Marked reduction in tumor appearances	165–166
Gerber et al[167]	Epidermal growth factor receptor inhibitor associated rash	49	10–20mg/day used in combination therapy	Used for severe or therapy-resistant rashes	Significant improvements	
Rabello-Fonseca et al[168]	Cosmetics and photoaging	30	10 or 20mg three times weekly		Preauricular biopsies demostrated significant increase in collagen fibers and decrease in elastin	
Akyol et al[2]	Icthyosiform dermatosis		0.5mg/kg/day	Most successful with lamellar and congenital icthyosiform erythroderma	High response rates noted	

Other uses include: erythroplasia of queyrat, dysplastic nevi, systematized epidermal nevi, extranodal Rosai-Dorfman disease, acanthosis nigricans, subcorneal pustular dermastosis, metastatic melanoma, morbihan disease.[2,37,169]

three patients with either extensive basal cell carcinoma (BCC) or SCC.[112] These studies suggest that isotretinoin might still be a valid adjunctive treatment option for advanced SCC.

ISOTRETINOIN'S USE AS A CHEMOPREVENTIVE AGENT IN HIGH-RISK POPULATIONS

Isotretinoin and other systemic retinoids have been implemented as chemopreventive agents in patients with prior histories of nonmelanoma skin cancer (NMSC) as well as in patients with certain genodermatoses, predisposing them to cancerous growths, such as xeroderma pigmentosa (XP) and nevoid basal cell carcinoma syndrome (NBCCS).[113–116]

Kraemer et al[115] demonstrated isotretinoin's chemopreventive benefits in XP. The three-year study of 12 patients resulted in a 63-percent drop in the appearance of new skin cancerous lesions. However, the dose was quite high

at 2mg/kg/day, and all of the patients experienced severe mucocutaneous toxicity and required a dose reduction. Later, lower doses ranging from 0.5 to 1.5mg/kg daily, based on individual response, were also shown to be effective.[117] Other small case studies are available that support the efficacy of isotretinoin in XP.[118,119] Continual therapy is required as tumor growth returns to normal rapidly upon discontinuation of isotretinoin.[117,120] Goldberg et al[116] initially demonstrated that 0.4mg/kg/day of isotretinoin could be beneficial in the treatment of NBCCS, as it was shown to reduce the appearance of new skin cancer lesions. However, additional reports have yet to be published with similar findings.

Isotretinoin has had more limited success in preventing NMSC in patients who do not have a specific genodermatosis that predisposes them to cancerous growth. In a large Phase 3 trial (n=525), Levine et al[121] found that daily isotretinoin (5–10mg/day) did not decrease the appearance of new cancerous lesions more than the placebo. This investigation involved 525 high-risk patients with prior histories of NMSC. A recent re-analysis of Levine's 1997 investigation and a comprehensive literature review on the chemopreventive benefits of retinoids have both restated that isotretinoin is ineffective in preventing NMSC in high-risk groups.[122,123]

Others have also demonstrated that isotretinoin is ineffective in preventing BCC in high-risk individuals.[124–126] Isotretinoin has also been implemented in combination with INF-α in adjunctive regimens in hopes of improving remission rates of NMSC. Unfortunately, this has also been shown to be rather ineffective as demonstrated in a recent Phase 3 trial of 66 patients with aggressive SCC.[127] In the study, patients received either 13-cis-retinoic acid (1mg/kg/d orally) and INF-α (3x106U) three times a week or no treatment. At the end of 21.5 months (median follow-up), it was determined that isotretinoin/INF-α did not improve tumor recurrence versus control (hazard ratio [HR], 1.13; 95% CI, 0.53 to 2.41), time to tumor recurrence (HR, 1.08; 95% CI, 0.43 to 2.72), or time to the appearance of a second primary tumor (HR, 0.89; 95% CI, 0.27 to 2.93).

ISOTRETINOIN'S USE IN COSMETICS AND PHOTOAGING

Topical isotretinoin has been used for many years with documented cosmetic benefits for photodamaged skin.[170–172] Although topical tretinoin is generally accepted as a cosmetically beneficial medication for photodamaged skin, oral isotretinoin is not. Recently, more trials have been completed to determine whether oral isotretinoin would have similar effects.

In 2000, Perez et al[173] noted significant cosmetic benefits with the addition of 10 to 20mg of isotretinoin three times weekly over two months in combination with skin rejuvenation cosmetic procedures when compared to the cosmetic procedures alone. Perez et al stated that there was a significant improvement in all patients taking isotretinoin in wrinkles, thickness and color of the skin, size of pores, skin elasticity, tone, reduction in pigmented lesions and mottled hyperpigmentation.

Additional evidence for cosmetic improvement was demonstrated by the Rabello-Fonseca et al[168] study of 30 female patients between 40 and 55 years old divided into two groups taking 10mg versus 20mg of isotretinoin three times weekly over three months. Biopsies from the left preauricular area were taken before and after treatment. A significant increase in collagen fibers were observed and a decrease in elastin was noted in the after treatment specimens. This study also reported visual improvement to skin texture, wrinkle depth, and color in both after treatment groups. There was no statistically significant difference between the two treatment groups.

There exists some debate about whether oral isotretinoin is effective for the treatment of photodamaged skin.[174] In challenge to these findings, Bagatin et al[175] studied 32 women between 40 and 55 years old divided into two groups. Group A (n=21) received 20mg of isotretinoin three times weekly, nightly moisturizer, and daily sunscreen, while Group B (n=11) used only the moisturizers/sunscreen combination. Clinically, there was noted improvement in both groups before and after treatment, but there was not a statistically significant difference between Group A and Group B. Biopsy specimens taken from the forearm of 10 patients selected randomly from Group A and all patients from Group B failed to show a significant difference in epidermal thickness, new collagen formation, or elastosis after treatment or between the two groups. There was a significant decrease in p53 expression noted in the after treatment specimens of Group A treated with oral isotretinoin.

CONCLUSION

Since its FDA approval in 1982, the use of isotretinoin in dermatological conditions other than acne has continued to increase. Its successful implementation in these conditions suggest that it has a broader spectrum of uses than was once considered. However, randomized clinical trials are still needed to help clarify when and how systemic isotretinoin should be employed. Presently, it is only considered in recalcitrant conditions and should be employed in accordance with the iPledge system and with proper and informed use about its side effect profile and its potential for teratogenicity. With judicious implementation, the future is sure to reveal additional uses to maximize the capacity of isotretinoin.

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