

Oral Isotretinoin and Its Uses in Dermatology: A Review

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Abstract: In 1982, the Food and Drug Administration (FDA) of the United States of America approved isotretinoin (13-cis-retinoic acid), a retinoid derivative of vitamin A, to treat severe recalcitrant acne vulgaris. Apart from its prescribed use for severe acne, evidence suggests that isotretinoin is commonly used off-label to treat mild-to-moderate acne, inflammatory skin conditions, genodermatoses, skin cancer, and other skin disorders. This is due to its anti-inflammatory, immunomodulatory, and antineoplastic properties. Some “off-label” use is successful, while others are ineffective. Therefore, this information is essential to clinicians for deciding on the appropriate use of isotretinoin. In this article, we aim to review the most updated evidence-based data about the use of oral isotretinoin in dermatology.

Keywords: isotretinoin, acne vulgaris, rosacea, skin cancer, dermatology

Introduction

Isotretinoin (13-cis-retinoic acid) is a retinoid derivative of vitamin A approved by the FDA of the United States and Europe (excluding Sweden) in 1982 and 1983, respectively. Its primary use is for treating severe recalcitrant cases of acne vulgaris.^{1,2}

Isotretinoin is a highly effective acne treatment. It works by reducing the size of sebaceous glands, lowering sebum excretion, regulating cell proliferation, and decreasing keratinization. Isotretinoin can alter the microenvironment of the follicles, resulting in a decrease in the number of *Cutibacterium acnes*.^{3,4} Additionally, it possesses anti-inflammatory and immunomodulatory properties by reducing monocyte TLR-2 expression, minimizing the inflammatory cytokine response, and antineoplastic properties, making it a valuable treatment option for various skin diseases.^{5,6}

According to data, a lot of isotretinoin is being utilized off-label to treat mild-to-moderate acne, inflammatory skin diseases, genodermatoses, skin cancer, and other skin disorders.^{7–9} Some “off-label” use is successful, while others are ineffective. Therefore, this information is essential to clinicians for deciding on the appropriate use of isotretinoin. This review aims to review the most updated evidence-based data about the use of oral isotretinoin in dermatology.

Use of Oral Isotretinoin in Acne

Although isotretinoin is labeled by FDA only for treating severe recalcitrant acne, there is a consensus among the expert’s opinion that patients with less severe acne who do not respond to conventional therapy and patients with scarring acne that causes severe psychologic distress may also be good candidates for this drug.¹⁰

Prognostic factors which should be considered for the early use of isotretinoin include a family history of severe acne, early onset of acne, hyper seborrhea, truncal acne, scarring acne, psychosocial problems, and persistent acne.¹¹

The conventional dosage of isotretinoin is 0.5 to 1 mg/kg/day in two divided doses with a standard cumulative dosage of 120 to 150 mg/kg/course. Managing patients with acne can vary based on different guidelines and consensus. The

recommended daily dosage ranges from 0.3 to 0.5 mg/kg in European guidelines, while US guidelines suggest up to 1 mg/kg. However, only the European guidelines recommend a minimum treatment duration of six months.¹²

Isotretinoin treatment should begin with a dose of 0.5 mg/kg; if the patient is well tolerated, increase the amount to 1 mg/kg, but if side effects cannot be taken, low dose or intermittent therapy can be used.¹³ The duration of therapy is about four to six months, depending on the daily dose that can be adjusted by clinical response and the side effects. Treatment discontinuation should be considered when the clinical severity score of acne has improved more than 90% compared to the beginning of treatment for one to two months.³

Clinical data suggest that the long-term cure rate after a course of isotretinoin may be lower than reported, especially in younger patients who have a chance to relapse more than older ones.^{3,14,15} A course of isotretinoin therapy can completely clear acne in 61% of patients, 39% relapsed within the first 18 months after treatment, and 23% required an additional course of isotretinoin.¹⁴ A study that followed 299 patients for five years after treatment revealed that 17% required two courses, 5% required three, and 1% required four to five courses of treatment. Contributing factors for more than one course of isotretinoin therapy included lower dose treatment regimens, severe acne, female over 25, and long history of acne.¹⁶

Despite the reports of relapses, this conventional regimen is still highly effective while at the same time causing several dose-related side effects. Therefore, micro-dose, mini-dose, low-dose, and intermittent treatment regimens with better tolerance and lower incidence of adverse effects have been introduced.^{12,17–25}

Although low-dose isotretinoin regimens are not yet the standard of care, several studies have reported their usage. However, due to the heterogeneity of these studies, there are no definitive criteria for determining the appropriate dosage of low-dose isotretinoin. Palmer defined micro-dose as continuous treatment with a single 20 mg isotretinoin tablet, taken once or twice weekly (0.04–0.11 mg/kg/day).²⁴ Amichai similarly used a mini-dose regimen by treating patients with 20 mg of isotretinoin weekly.²⁵ Strauss classified three different dosing levels of isotretinoin into low-daily dose (0.1 mg/kg/day), intermediate-daily dose (0.5 mg/kg/day), and high-daily dose (1 mg/kg/day).²⁶ Al Muqarrab described a low-daily dose regimen as a short course of 0.1–0.3 mg/kg/day and the pulsed dose regimen as the intermittent use of isotretinoin (every other day low dose or monthly low dose pulses).²⁷

A systemic review and meta-analysis of ten randomized controlled trials (RCTs) involving 809 patients with acne vulgaris that compared low-daily doses with a conventional dose showed an overall favorable benefit of conventional dose (SMD 0.35, 95% CI - 0.29–0.99, $p = 0.28$) with a better effect on preventing relapse (OR 1.63, 95% CI 0.51–5.21, $p = 0.02$).²⁶

Contrarily, a systemic review of fifteen studies, comprising 3 prospective, 2 retrospective, 8 RCTs, and 2 articles with unspecified details, has confirmed that daily dosages ranging from 0.1 to 0.3 mg/kg can be recommended as a viable option for the treatment of acne vulgaris, considering their minimal side effects and cost-effectiveness, albeit with a higher probability of relapse. For greater effectiveness, oral isotretinoin should be combined with topical medications such as tretinoin, adapalene, and clindamycin.²⁸

Other literature reviews demonstrated that the efficacy and relapse rates of low-dose regimen in mild-to-moderate grades of acne are comparable with the conventional regimen (1 mg/kg/day), which is given in the severe grade of acne vulgaris.^{21,29,30} An RCT revealed that the conventional (0.5–0.7 mg/kg/day) and low-dose (0.25–0.4 mg/kg/day) regimens have similar efficacy, while intermittent treatment (0.5–0.7 mg/kg/day for one week out of every four weeks) had less effective than conventional or low-dose regimens.³¹

Different results could be from different study methodologies and the heterogeneity of the study groups. Further RCTs with adequate sample sizes, longer follow-up periods, and analysis outcomes regarding the cumulative dose rather than the daily dose of isotretinoin in mild-to-moderate acne patients are required.²⁷ While there is still no definitive conclusion on the effectiveness of low-dose isotretinoin therapy for mild-to-moderate acne vulgaris, extensive evidence suggests that a low-dose regimen over a longer period of time has shown more significant outcomes and long-term remission, highlighting the need for higher cumulative doses.^{21,27,30}

In addition to conventional-dose and low-dose regimens, high-dose regimens and regimens that adjust treatment according to the patient's response have also been proposed. A prospective, observational intervention study in 80 patients with nodulocystic acne treated with high-dose isotretinoin with a mean daily dose of 1.6 mg/kg for an average of

178 days (cumulative dose 290 mg/kg) showed all patients were resolved from acne upon completion of treatment. During the three-year follow-up period, only ten patients (12.5%) developed a relapse that required an additional course of isotretinoin.³²

Coincided by another study that included 116 acne patients in the 12-month follow-up survey indicated that the relapse rate was 47.4% in the lower-dose treatment group (accumulative dose <220 mg/kg) compared with 26.9% in the high-dose group (accumulative dose \geq 220 mg/kg) ($P = 0.03$). Although almost 100% of the patients in both groups developed cheilitis and xerosis during treatment, this study suggests that significantly higher doses of isotretinoin are effective for treating acne and decreasing relapse rates.³³

Adjusting treatment according to the patient's response regimens was studied in 132 patients. Every patient was treated with isotretinoin 0.75 mg/kg/day until all active inflammatory lesions were cured, followed by a maintenance dose of 20 mg/day for one more month. Treatment was continued for 6.6 ± 2.5 months with a cumulative dose of 111.5 ± 33.9 mg/kg. The mean final improvement rate was 96.7% (95% CI, 84.9% to 108.5%). Only 18.35% of the patients experienced relapse after a mean interval of 1.28 years.³⁴

Isotretinoin is poor water solubility that limits oral bioavailability and requires a high-fat (50gm fat) and high-calorie (800–1000 calories) meal for better absorption.³⁵ The bioavailability of isotretinoin increased 1.5 to 2 times more significantly when the dose was administered 1 hour before, concomitantly with, or 1 hour after a meal than when it was taken during a complete fast.³⁶ This recommendation cannot be followed in many patients, which may result in poor treatment efficacy.

Two new formulations of isotretinoin can increase gastrointestinal absorption by a lipid-based drug delivery system resembling a fatty meal (Lidose-isotretinoin) and accelerating dissolution by particle micronization (Micronized-isotretinoin).³⁷ When taken with food, Micronized-isotretinoin 32 mg and Lidose-isotretinoin 40 mg have the same bioequivalence. However, when taken in a fasted state, Micronized-isotretinoin 32 mg is absorbed at approximately twice the rate of Lidose-isotretinoin 40 mg.³⁸ A randomized, multicenter, double-blind study in 600 patients with severe recalcitrant nodular acne demonstrated that once-daily use of the Micronized isotretinoin (0.4mg/kg/day) under fasted conditions is clinically comparable to the conventional dose isotretinoin (1mg/kg/day) under fed conditions.³⁹ New formulations enhanced the absorption and bioavailability of isotretinoin with food independence helping patients achieve optimal cumulative dosing that reduces acne lesions and relapse rates.⁴⁰

While there may be variations in the guidelines and consensus regarding the treatment of acne patients,¹² the accumulative dose over the entire course of treatment was found to be a significant factor in preventing relapse.^{41,42} According to a study on the factors that contribute to relapse after undergoing oral isotretinoin treatment (dosage of 0.3–1 mg/kg/day for a minimum of four months), it was discovered that the relapse rate stands at 37.3%. Patients who are younger than 20 years old, have macrocomedone-type acne or have remaining lesions after treatment are more likely to experience a relapse. The median time for relapse is ten months.⁴³

Evidence from RCTs of isotretinoin in acne treatment is summarized in Table 1.

Use of Oral Isotretinoin in Inflammatory Skin Diseases

Rosacea

Rosacea is a chronic inflammatory skin disease characterized by recurrent flushing, persistent erythema, papules, pustules, and telangiectasia on facial skin and eyes. Inflammatory pathways associated with rosacea pathogenesis include immune system dysregulation and neurocutaneous mechanism.⁵⁵ Isotretinoin can be used in treating rosacea because it reduces sebocyte proliferation, sebum production, inflammation process, and telangiectasia on the skin.^{3–5,56} Also, isotretinoin modifies the skin microenvironment and changes the density of *Demodex folliculorum*, which is associated with rosacea.⁵⁷ A review of 15 studies with a total of 991 patients who were treated with isotretinoin for rosacea confirmed its effectiveness. The dosages ranged from 0.22 to 1 mg/kg/day, with 0.3 mg/kg/day being the most effective in achieving complete remission after 12 weeks of therapy.⁸ Studies proved that isotretinoin is more effective in decreasing rosacea symptoms than placebo, topical tretinoin, doxycycline, and minocycline.^{58–61} A retrospective study demonstrated that low-dose isotretinoin (40 mg/week) was more effective than minocycline (100 mg/day) for severe rosacea, achieving a complete response in 62.5% of patients after 4–7 months of treatment.⁶¹ A study found that patients

Table 1 Oral Isotretinoin and Its Uses in Acne

Author and Year	Study	Number of Patients	Treatment Regimen	Results
Agarwal US et al 2011 ⁴⁴	Compare the efficacy and tolerability of oral isotretinoin in daily, alternate, pulse, and low-dose regimens	N=112	A. 1 mg/kg/day B. 1 mg/kg alternate day C. 1 mg/kg/day for 1 week out of every 4 weeks D. 20 mg every alternate day • 6 weeks – Follow 8 weeks	<ul style="list-style-type: none"> • Comparable efficacy in A, B, and D • Severe acne is better in A than B, C, and D • Moderate acne is better in A, B, and D • Mild acne had almost similar results in all groups
Lee JW et al 2011 ³⁰	Compare the efficacy of low-dose and intermittent doses with conventional dose isotretinoin	N=60	A. 0.5–0.7 mg/kg/day B. 0.25–0.4 mg/kg/day C. 0.5–0.7 mg/kg/day for 1 week out of every 4 weeks • 24 weeks – Follow 1 year	<ul style="list-style-type: none"> • Comparable efficacy in A and B • C had less effect than A and B • Relapse in 1 year; C > B > A
Boyras N, Mustak PK 2013 ⁴⁵	Compare the efficacy of intermittent and continuous low-dose isotretinoin regimens in moderate acne vulgaris	N=60	A. 20 mg/day B. 0.5–0.75 mg/kg/day for 1 week every month • 6–8 months • Follow 6 months	<ul style="list-style-type: none"> • Comparable efficacy in A and B • Relapse in 6 months; B > A
Webster GF et al 2013 ⁴⁶	Open-label, single-dose, randomized, 4-treatment, crossover comparative isotretinoin VS Lidose-isotretinoin	N=60	A. Lidose-isotretinoin (2 × 20 mg) in a fast state B. Lidose-isotretinoin (2 × 20 mg) in a fed state C. isotretinoin (1 × 40 mg) in a fast state D. isotretinoin (1 × 40 mg) in a fed state	<ul style="list-style-type: none"> • Both formulations were bioequivalent in the fed state • Mean plasma levels of Lidose-isotretinoin almost twice as much isotretinoin in a fasting state
Rademaker M et al 2014 ⁴⁷	Compare the efficacy of isotretinoin 5 mg daily with placebo for low-grade acne vulgaris	N=58	A. 32 weeks of 5 mg/day B. first 16 weeks of placebo, followed by 16 weeks open-label 5 mg/day • Follow 10 weeks	<ul style="list-style-type: none"> • A improved within 4 weeks and continued during 32 weeks of treatment • Similar results are only seen in B from week 20 (4 weeks after starting isotretinoin)
Niazi S, Shehzad A 2015 ⁴⁸	Compare the efficacy of alternate-day fixed low-dose with daily low-dose isotretinoin in mild to moderate acne vulgaris	N=60	A. 20mg/day B. 20mg on alternate days • 6 months	In A, efficacy was 90%, whereas, in B, efficacy was 86.7% (P>0.05)

Ahmad HM 2015 ⁴⁹	Compare the efficacy of single versus twice daily dose isotretinoin for acne vulgaris (mild to severe)	N=58	All patients received 0.5–1.0 mg/kg/day A. once daily dose B. twice-daily dose • 5 months	<ul style="list-style-type: none"> Both resulted in highly significant clinical improvement with no significant difference Side effects were significantly more common in A
Dhaked DR et al 2016 ²²	Compare the efficacy of two low-dose oral isotretinoin, 20 mg daily and 20 mg alternate days, in moderate to severe acne vulgaris	N=234	A. 20mg/day B. 20mg on alternate days • 24 weeks • Follow 12 weeks	<ul style="list-style-type: none"> In severe acne, A performed significantly better than B In moderate acne, a significantly better in A was observed only up to 12 weeks, whereas, at the end of therapy, the response was the same in both groups
Santoshkumar A Shetti et al 2017 ⁵⁰	Compare the efficacy of the low-dose continuous and intermittent isotretinoin in the treatment of moderate-to-severe acne vulgaris	N=100	A. 20 mg/day B. 20 mg/day for 1 week out of every 4 weeks • 4 months • Follow 6 months	<ul style="list-style-type: none"> A has better clinical efficacy than B ($P < 0.005$) Higher recurrence rate in B
Faghihi G et al 2017 ⁵¹	Compare the efficacy of low dose with conventional dose isotretinoin in moderate and severe acne vulgaris	N=60	A. 0.5 mg/kg/day B. low-dose 0.25 mg/kg/day • 6 months • Follow 6 months	The average improvement of acne in A and B did not differ significantly within any of the study periods ($P > 0.05$)
El Aziz Ragab MA et al 2018 ⁵²	Investigate the effects of low-dose and conventional-dose isotretinoin on dermcidin expression in acne vulgaris patients	N=30 moderate-severe acne vulgaris patients and 15 healthy controls	A. low-dose (20 mg/day) B. conventional high dose (0.5 mg/kg/day) • Skin biopsies at the start of the study and 6 months later • Follow 12 months	<ul style="list-style-type: none"> The percentage of improvement was significantly related to the percent increase in dermcidin ($p < 0.001$) in both groups Relapse after 12 months was not statistically different among both regimens ($p = 0.464$)
Pandey D, Agrawal S 2019 ⁵³	Compare the efficacy of combining isotretinoin and antihistamine to isotretinoin alone in moderate to severe acne vulgaris	N=80	A. isotretinoin 0.5–0.6 mg/kg/day B. isotretinoin 0.5–0.6 mg/kg/day with levocetirizine 5 mg/day just before sleep • 12 weeks	B showed a more statistically significant decrease in GAGS score ($p=0.005$) and inflammatory lesions ($p= 0.010$) with less adverse effect and less flare-up
Kassem B et al 2022 ⁵⁴	Compare the efficacy of conventional, low, and intermittent isotretinoin dosage in moderate acne vulgaris	N=107	A. 0.5–1 mg/kg/day B. 0.25–0.4 mg/kg/day C. 0.5–0.7 mg/kg/day for 1 week out of every 4 weeks • 24 weeks	<ul style="list-style-type: none"> Significant differences in GAGS scores were found between B and C ($p = 0.037$) and between A and C ($p < 0.001$), while no significant differences between A and B ($p = 0.153$) GAGS was found to be a better predictor of relapse than age ($p < 0.001$)

Abbreviation: GAGS, global acne grading system.

with mild-to-moderate papulopustular rosacea who were treated with a very low dose of isotretinoin (10–20 mg once to five times a week, equivalent to 5 mg/day) for 57 weeks experienced a 91% clearance of their rosacea.⁶² However, it was also reported that high relapse rates (45–58.3%) occurred within 11 months after isotretinoin treatment in rosacea.^{60,63}

Recently, patients with Morbihan disease, a rare complication of rosacea that results in an erythematous, edematous plaque on the face, have been reported to experience complete recovery without recurrence when taking oral isotretinoin at a daily dosage of 20–80mg.⁶⁴

Evidence from RCTs of isotretinoin in rosacea is summarized in Table 2.

Hidradenitis Suppurativa (HS)

It has been proposed for a long time that apocrine glands play a significant role in causing HS, but there is a lack of conclusive evidence to support this hypothesis. HS is a chronic inflammatory skin disease of the pilosebaceous unit in intertriginous body areas, such as the axilla and groin, and is characterized by persistent abscesses, comedones, fistulas, scars, and keloids. It is traditionally thought that HS and acne are closely related, and because of this, isotretinoin has also been used in treating HS. There is an assumption that oral isotretinoin effectively treats HS by reducing follicular plugging.⁶⁵

There have been variable responses of HS to isotretinoin in the literature. Three retrospective studies showed that 15.9–68% of patients had clinical improvement as early as four months, especially female gender, and acne history was associated with a positive response to oral isotretinoin doses ranging from 0.45 mg/kg/day to 140mg/day.^{66–68} A recent retrospective study revealed that 35.9% of patients responded to treatment and had a positive association with pilonidal cyst history but not associated with the patient's BMI, Hurley stage, or history of acne.⁶⁹

On the contrary, some patients reported worsening HS by increasing several inflammatory nodules following isotretinoin treatment.^{67,70} Eight patients with severe acne treated with isotretinoin and subsequently developed HS have been reported.⁷¹

However, there is evidence demonstrating that isotretinoin could be used as an effective alternative or adjunctive therapy in early inflammatory lesions of HS.^{66–68,72}

Table 2 Oral Isotretinoin and Its Uses in Rosacea

Author and Year	Study	Number of Patients	Treatment Regimen	Results
Ertl GA et al 1994 ⁵⁸	Compare the efficacy of topical tretinoin and low-dose oral isotretinoin in rosacea	N=20	A. isotretinoin (10 mg/d) B. topical tretinoin (0.025% cream) C. combination A and B • 16 weeks • Follow 16 weeks	• A showed a more rapid onset of improvement, but there were no differences between the groups after 16 weeks • Improvement continued during the following 16 weeks
Gollnick H et al 2010 ⁵⁹	Compare the efficacy of oral isotretinoin, doxycycline, and placebo in rosacea	N=549	A. isotretinoin (0.1 mg, 0.3 mg, or 0.5 mg/kg/day) B. doxycycline (100 mg daily for 14 days, then 50 mg daily) C. placebo • 12 weeks	• Complete remission in 24% and improvement in 57% of A • Complete remission in 14% and improvement in 57% of B
Sbidian E et al 2016 ⁶⁰	Compare oral isotretinoin (0.25 mg/kg/day) with placebo (2:1 ratio) for difficult-to-treat papulopustular rosacea	N=156	A. isotretinoin (0.25 mg/kg/day) B. placebo • 4 months • Follow 4 months	• 57.4% of A and 10.4% of B had more than a 90% decrease in papules and pustules • 58.3% of A relapse with a median of 15 weeks

Folliculitis Decalvans (FD)

FD is a chronic neutrophilic inflammation of hair follicles characterized by irregular scarring alopecia, follicular hyperkeratosis, multiple pustules, perifollicular crusts, and tufted hair folliculitis on the scalp. Pathophysiology is unknown but considered an abnormal immune response to *Staphylococcus aureus*. Isotretinoin plays a role in FD treatment through the direct immunomodulatory effect that can inhibit the migration of neutrophils into the skin.

A total of 89 patients with FD were included in four retrospective studies and two case reports. They were treated with oral isotretinoin for 5–7 months, with doses ranging from 0.1 to 1.02 mg/kg/day. In many cases, the treatment was combined with antibiotics such as clindamycin, cephalexin, minocycline, rifampicin, and dapsone or prednisolone.^{73–78} Most patients (82–90%) reached a partial or complete response within three months and remained in remission for four months to two years.^{73,74} In a retrospective study, it was found that oral isotretinoin monotherapy led to complete healing in 82% of patients. Those who took oral isotretinoin at a dosage of ≥ 0.4 mg/kg/day for more than three months had a better response rate. Of the responders, 66% never experienced a relapse.⁷⁴ However, an isotretinoin refractory case of FD has been reported after treatment up to 60 mg/day for three months but successfully with biosimilar adalimumab.⁷⁷

Dissecting Cellulitis (DCS)

DCS is characterized by perifollicular, follicular pustules and nodules that develop into tracts coalescing into chronically inflamed tissue that end up with scarring alopecia. The effectiveness of isotretinoin may be due to its sebaceous gland suppression, anti-inflammatory effect, and normalization of follicular keratinization.⁷⁹

A review and meta-analysis included five retrospective studies from 2004 to 2018, demonstrating that the overall efficacy of isotretinoin for DCS was estimated to be 0.9 with a 95% CI (0.81–0.97). Most patients improved or completed remission. Recurrence was seen in 24% (6/25) of patients.⁸⁰ The most successful treatment study used a 0.5–0.8 mg/kg/day dosage with an average treatment duration of 3 months.⁸¹ The relapse of DCS is a common finding for those who undergo successful treatment. Retreatment with isotretinoin after relapse is still effective.⁸² Maintenance therapy with 0.75–1 mg/kg/day has been proposed to prevent the high recurrence rates.⁸³ Similar results have been found in two systematic reviews. The first review from 57 articles, including 90 patients, revealed that approximately 54% of all patients treated with isotretinoin showed significant improvement, but 19% eventually relapsed.⁸⁴ The second review from 14 studies with 76 patients reported most patients (71.1%) had significant clinical improvement with isotretinoin dosages ranging from 0.27 to 1 mg/kg/day for several months, while 29.9% had no improvement, and relapse was reported in two patients.⁸ Successful treatment with low-dose isotretinoin (0.25 to 0.5 mg/kg/day) has also been reported in 65 out of 72 (90.3%) patients with DCS.⁸⁵

Seborrheic Dermatitis (SD)

There are few studies on the treatment of SD with oral isotretinoin. A retrospective study demonstrated that all 48 patients with moderate-to-severe SD treated with either 20 mg or 10 mg daily of oral isotretinoin for 2 to 6 months showed a significant reduction in the symptom scale of seborrheic dermatitis score compared with baseline. Additionally, there was no significant difference between the outcomes of these two groups.⁸⁶ An RCT compared isotretinoin 10 mg every other day and topical treatment in 45 patients with moderate-to-severe SD revealed that isotretinoin significantly decreased scalp pruritus, sebum production, and increased quality of life than topical treatment.⁸⁷ Recently, a systematic review showed that isotretinoin treatment is more effective than oral itraconazole, anti-fungal shampoo, or salicylic acid-containing soap in improving SD symptoms, even at low doses. Isotretinoin is a potentially effective treatment for moderate-to-severe SD and is generally well tolerated and safe.⁸⁸

On the contrary, a retrospective study has revealed that 5 patients who underwent effective isotretinoin therapy for their acne subsequently suffered from seborrheic dermatitis-like skin eruptions.⁸⁹

Psoriasis

Psoriasis is a chronic inflammatory skin disease classified as plaque, pustular, and erythrodermic. Isotretinoin can modulate abnormal hyperproliferation, differentiation of keratinocytes, and inflammatory cells in psoriasis.⁸ A prospective cohort study

compared the efficacy of isotretinoin (30 mg twice daily) with methotrexate (5 mg thrice weekly) in patients with moderate-to-severe plaque psoriasis for 12 weeks revealed that isotretinoin is effectively less than methotrexate when compared with the mean percentage reduction in PASI score (52.78 ± 7.34 and 70.23 ± 6.78).⁹⁰ Successful treatment of plaque-type psoriasis with combination therapy between isotretinoin and phototherapy has been reported in two RCTs. The first study compared narrow-band ultraviolet B (NBUVB) + isotretinoin (0.5 mg/kg/day) with the control group receiving NBUVB + placebo demonstrated that isotretinoin + NBUVB could reduce the number of phototherapy sessions and cumulative NBUVB dose.⁹¹ The second study showed that combining isotretinoin (0.5 mg/kg/day) with oral psoralen + sun exposure (PUVAso) is more effective than PUVAso alone for treating chronic plaque psoriasis.⁹² A case series documented that five individuals with generalized pustular psoriasis did not respond to conventional therapy but were effectively treated with isotretinoin (1.5–2 mg/kg/day) within a short treatment period.⁹³ A comparative study revealed that even though the efficacy of isotretinoin and etretinate in treating generalized pustular psoriasis was comparable, isotretinoin was less effective than etretinate in treating chronic plaque psoriasis.⁹⁴

Pityriasis Rubra Pilaris (PRP)

PRP refers to skin conditions characterized by follicular hyperkeratotic papules and reddish-orange scaling patches with well-defined borders. The effectiveness of isotretinoin can be attributed to its ability to normalize keratinization.

According to a review of eleven studies, 122 patients were treated with oral isotretinoin at doses ranging from 0.5 to 4 mg/kg/day. The results showed that most patients (82%) responded well to treatment with 50–90% lesion clearance. These positive outcomes were observed over treatment periods ranging from 1 to 6 months. However, relapse was seen between 4 and 12 weeks after the end of treatment.⁸ There has been a report of two cases of PRP following the administration of the ChAdOx1 (COVID-19) vaccine were successfully treated with a combination of isotretinoin (20 to 30mg) and emollients for three months, resulting in complete remission.⁹⁵ Same as a recent case series report revealed the effective use of isotretinoin (10–20 mg/day for 6–12 weeks) in treating two cases of PRP that were initially misdiagnosed as atopic dermatitis.⁹⁶

Cutaneous Lupus Erythematosus (CLE)

CLE is classified as acute, subacute, and chronic. Isotretinoin can be used by decreasing inflammatory processes and reducing abnormal hyperproliferation of keratinocytes.

A study demonstrated that 86.9% of 24 patients with chronic or subacute CLE treated with isotretinoin 0.15–0.5 mg/kg/day showed improvement or clearing of clinical lesions and histopathology within 16 weeks. Better results were seen in patients with chronic CLE.⁹⁷ A review of seven studies on isotretinoin monotherapy (10 to 50 mg/day) in 19 patients with CLE showed that 90% of the skin lesions displayed signs of improvement within one to three months.⁸ Combination therapies isotretinoin (0.5 to 1.5 mg/kg/day) with hydroxychloroquine, prednisone, topical clobetasol propionate, and fluocinonide also showed high efficacy of treatment by all patients showed 90% improvement in only three weeks.^{98–100}

However, it has been reported in a case series of six patients that discontinuing treatment resulted in a rapid recurrence of lesions.⁹⁹

Lichen Planus (LP)

Isotretinoin may be effective in lichen planus by regulating cellular proliferation and differentiation of keratinocytes.

According to various reports, mucocutaneous LP has shown a positive response to oral isotretinoin at a dosage of 0.25–1 mg/kg/day, with noticeable clinical improvement within two months of treatment.⁸ However, two reports showed relapse in five patients within two months after discontinuing treatment.^{101,102} Successful prevention of relapse by oral isotretinoin 20 mg alternate days for another month has been reported.¹⁰³ A prospective study of the efficacy of fixed low-dose isotretinoin (20 mg/day) for six months in oral and cutaneous lichen planus pigmentosus showed moderate improvement (25–50%) and good improvement (>50%) in 55.7% and 21.8% of the patients, respectively.¹⁰⁴

Lichen Planopilaris (LPP)

LPP is an uncommon inflammatory condition characterized by lymphocytic infiltration and fibrosis that can lead to cicatricial alopecia. One form is frontal fibrosing alopecia (FFA), which affects the frontotemporal hairline with facial papules. Isotretinoin may play a role by normalization of follicular keratinocyte antigen expression and reducing inflammatory cellular infiltrate.¹⁰⁵

A review, including three retrospective cohort studies and three case series, has shown that oral isotretinoin can effectively treat LPP. Successful outcomes have been observed with dosages ranging from 10 mg every other day to 40 mg/day and treatment durations ranging from 2 to 24 months.⁸ A comparative study showed no further progression of LPP in 76% of patients and no relapse in 72% after isotretinoin treatment (20mg/day) for 12 months.¹⁰⁶ According to an RCT, patients with facial LPP showed greater improvement when taking oral isotretinoin (20 mg/day) than those using topical 0.05% isotretinoin gel.¹⁰⁷ Combining Isotretinoin with 5-alpha reductase inhibitors, finasteride, spironolactone, pimecrolimus cream, and vitamins has proven to be highly effective in treating both LPP and FAA.^{108,109}

Granuloma Annulare (GA)

GA is a common inflammatory skin disease that may be caused by a delayed hypersensitivity reaction in the dermis, typified clinically by annular, smooth, purplish papules and plaque. Isotretinoin has a role in GA through its anti-inflammatory effect and altered cellular proliferation.¹¹⁰

Sixteen patients with GA, including generalized, localized, and perforating types, showed 90% clinical improvement after being treated with isotretinoin for three months to 1 year at a dosage of 0.5–1 mg/kg/day.⁸ However, recurrence occurred in 25% of all patients followed-up after discontinued treatment.^{111–113}

There have been reported cases of resistance to isotretinoin. It is recommended to only use isotretinoin for patients with disseminated or refractory GA.¹¹⁰

Use of Oral Isotretinoin in Skin Cancer

Basal Cell Carcinoma (BCC)

BCC is the most common, locally invasive skin cancer. According to various reports, BCC lesions experienced a 36–50% reduction, partially or completely, after undergoing treatment with oral isotretinoin monotherapy 0.2–8.2 mg/kg/day lasting two months to one year.⁸ In terms of skin cancer prevention, an RCT involving 981 patients with two or more previous BCC treated with 10 mg/day oral isotretinoin for 36 months showed no differences compared to the placebo in the cumulative percentage of patients with BCC at a new site or the annual rate of BCC formation existed.¹¹⁴ Concurred by another RCT in 525 patients with a history of BCCs and SCCs showed no difference between those who received retinol (25,000 units), isotretinoin (5–10 mg), or the placebo daily for three years in the time to the first occurrence or the total number of BCC or SCC reported.¹¹⁵

Squamous Cell Carcinoma (SCC)

SCC is a common type of invasive skin cancer derived from cells within the epidermis that can metastasize. Oral isotretinoin monotherapy dosages ranging from 0.5 to 3 mg/kg/day are used in many case reports for SCC treatment. Regression in 35.3% of SCC lesions can be observed as soon as two weeks after treatment.⁸ In a prospective study, thirty-two patients with inoperable SCC were treated with a combination of oral isotretinoin (1 mg/kg/day) and subcutaneous recombinant human IFN alpha-2a (3 million units/day) for at least two months showed a response rate 93% (13 of 14) in patients with advanced local disease (six complete responses), 67% (4 of 6) in patients with the regional disease (no complete responses), and 25% (2 of 8) in patients with distant metastases (one complete response).¹¹⁶ The similar result was observed in another clinical trial, isotretinoin (0.6–1 mg/kg/day) combined with alpha-IFN (6×10^6 I.U./day) for three months in 35 patients with SCC demonstrated a response rate in 41% of cases (13/32 evaluable patients) with five complete and eight partial responses.¹¹⁷

Leukoplakia

Leukoplakia appears as thick, white patches on the oral mucosa and can also be a sign of precancerous lesions in the mouth. An RCT has revealed that isotretinoin at a 2 mg/kg/day dose for three months is significantly more effective than a placebo in treating oral leukoplakia. The treatment resulted in a remarkable reduction in lesion size (67% vs 10%) and histologic dysplasia (54% vs 10%). However, after the treatment ended, relapse was observed in 56% (9 out of 16) of patients within three months.¹¹⁸

A clinical trial shows that low-dose isotretinoin (0.5 mg/kg/day) is more effective than beta-carotene (30 mg per day) in preventing leukoplakia. After nine months, 92% of patients using isotretinoin had stable lesions, while only 45% of patients using beta carotene had the same outcome.¹¹⁹ Recently, a systematic review and meta-analysis study of 8 RCTs conducted from 2008 to 2016 found no significant difference in clinical responses between chemo-preventive agents, like isotretinoin, and placebo for oral leukoplakia prevention.¹²⁰

Keratoacanthoma (KA)

KA is a rapidly growing destructive skin tumor that clinically may be indistinguishable from well-differentiated SCC. A case report of recurrent KA after surgical excision showed complete clinical resolution confirmed by skin biopsy after being treated with isotretinoin 1 mg/kg/day for 12 weeks.¹²¹ According to other reports, five patients with different types of KA (such as multiple KAs, giant KA, and KA centrifugum marginatum) were treated with oral isotretinoin 0.5–6 mg/kg/day and experienced regression as early as two weeks. However, it was common for this condition to recur within 8–12 weeks after the therapy was stopped.^{122–126} There have been reports of successful use of isotretinoin 0.25 mg/kg/day as a maintenance therapy to prevent new KA.¹²⁵

Cutaneous T-Cell Lymphoma (CTCL)

CTCL is the most common type of primary cutaneous lymphoma in which malignant T-cells are initially increased in the skin. Isotretinoin may play a role by changing multiple signaling pathways in cellular differentiation and apoptosis.

Studies on oral isotretinoin monotherapy for CTCL have shown that 1–2 mg/kg/day for 2–3 months is the most effective for achieving clinical remission. In combination therapy, a dosage of 1 mg/kg/day for 3–4 months has been found to be the most effective.⁸ In a clinical trial, isotretinoin and etretinate were compared in treating CTCL. After two months of treatment with isotretinoin at a dosage of 0.2–2 mg/kg/day, complete remission was observed in 21% of patients, while partial remission was in 38%. The study found that isotretinoin and etretinate had the same effectiveness in treating CTCL. However, despite continued therapy, 25% of patients experienced a relapse.¹²⁷ The combination of isotretinoin (0.5–1.5 mg/kg/day), etretinate, and PUVA therapy showed better results. The treatment led to complete remission in 73% of patients and partial remission in 27%.¹²⁸ A case study has confirmed the efficacy of using isotretinoin (20mg/day) as part of combination therapy with methotrexate and PUVA for early-stage refractory CTCL.¹²⁹ Additionally, six patients with advanced refractory folliculotropic mycosis fungoides have been successfully treated with IFN- γ in combination with low-dose oral isotretinoin (10–20mg/day), topical carmustine ointment, and phototherapy.¹³⁰

Use of Oral Isotretinoin in Genodermatosis

Xeroderma Pigmentosum (XP)

XP is a skin condition sensitive to ultraviolet light, leading to premature aging of the skin and an increased risk of developing skin cancer. Five XP patients were treated with oral isotretinoin at 2 mg/kg/day in a three-year controlled prospective study. The study found a 63% decrease in tumor occurrence during the two years of treatment. However, 60% of patients experienced an 8.5-fold increase in annual tumor occurrence within three months after treatment discontinuation.¹³¹

Successful treatment of combination therapy with isotretinoin (1 mg/kg/day) and chemotherapy in two cases of XP by completely resolved SCC without recurrence have been reported.^{132,133} High-dose oral isotretinoin (2 mg/kg/day) can reduce the number of skin tumors in XP and should only be used in patients with an exceptionally high number of newly

developed skin tumors, while some cases may respond to an intermediate dose (1 mg/kg/day) or a lower dose (0.5 mg/kg/day) of oral isotretinoin with fewer adverse effects.¹³⁴

Ichthyosis

Ichthyosis is a genetic skin disorder that can cause dry, itchy, scaly, rough, and red skin. Symptoms can vary in intensity. A multicenter clinical trial demonstrated that almost all patients with lamellar ichthyosis and epidermolytic hyperkeratosis could be improved with oral isotretinoin (mean dosage 2mg/kg/day). More significant improvement was seen in the group of patients with lamellar ichthyosis.¹³⁵ A case report revealed that isotretinoin treatment from day 7 of life could increase survival in a patient with harlequin ichthyosis.¹³⁶ The beneficial effects of isotretinoin in ichthyosis are dose-dependent. The mean dosing from the studies was 1.8 to 2.1 mg/kg/day, given the cutaneous and extracutaneous toxicities. A lower dose of 0.5–1 mg/kg/day is recommended for maximal clearing and maintenance with minimal side effects.¹³⁷

Darier's Disease (DD)

DD is an autosomal dominant genetic disorder with scaly crusted papules in a seborrheic distribution and skin folds. Isotretinoin may be efficacious by reducing abnormal proliferation and differentiation of the keratinocyte.

In eight studies involving 119 patients who used oral isotretinoin at doses of 0.5 to 4 mg/kg/day, it was observed that there was a significant improvement in lesions, ranging from 75% to 100%, within 4 weeks to 3 months. However, every patient who was followed up reported a relapse of lesions, ranging from 80% to 100%, within seven days to 6 months after stopping treatment.⁸ A comprehensive review of the therapeutic option for DD from 113 studies identified grade B evidence quality support for isotretinoin and suggested that taking isotretinoin continuously on maintenance dosing may be necessary to prevent a recurrence.¹³⁸

Use of Oral Isotretinoin in Cutaneous HPV Infections

Wart

Oral isotretinoin can be used in cutaneous HPV infections from the immunomodulatory effect inducing apoptosis, down-regulating HPV transcription in affected keratinocytes, and affecting epithelial differentiation and proliferation.¹³⁹

There has been a first report about an immunosuppressed patient who had developed persistent warts on their hands and feet after undergoing chemotherapy and showed clinical improvement after a 28-week treatment with oral isotretinoin at 1 mg/kg/day.¹⁴⁰ Complete remission was reported in fourteen patients with recalcitrant warts by combining low-dose isotretinoin (0.1–0.2 mg/kg/day) and topical therapy for 3 months with no sign of relapse for up to 3 years.¹⁴¹ The successful treatment of extensive and recalcitrant warts in an immunocompetent patient using isotretinoin monotherapy at 1mg/kg/day for six weeks has been reported. The patient remained in complete remission for 23 months with no signs of relapse.¹³⁹ An RCT demonstrated a statistically significant difference in the therapeutic response between the isotretinoin and the placebo groups, with complete clearance in 60% and 0% of the patients, respectively.¹⁴² A systematic review and meta-analysis revealed that combinations of systemic isotretinoin with intralesional immunotherapy yield higher complete clearance rates with lower recurrence.¹⁴³ Different results were found in a comparative study that showed no statistically significant difference between the combination of intralesional purified protein derivative (PPD) with a low dose isotretinoin and PPD alone regarding the therapeutic response.¹⁴⁴

Flat Wart

Several patients have reported positive outcomes from treatment with oral isotretinoin in the range of 0.1 to 0.5 mg/kg/day for flat warts.⁸ According to three RCTs, isotretinoin has proven to be effective. In one study, 16 patients treated with 30 mg/day of isotretinoin showed complete clearance of all recalcitrant flat warts within 12 weeks, while there was no improvement in the placebo group.¹⁴⁵ In the second study, patients who received a daily dose of oral isotretinoin at 0.5 mg/kg showed complete remission in 69% of cases. In contrast, only 38% of patients treated with topical isotretinoin 0.05% showed the same results after three months.¹⁴⁶ The third study found that 44.4% of patients in the oral isotretinoin

alone group (0.3 mg/kg/day) experienced complete clearance of flat warts, compared to 38.8% in the combination therapy with the Candida antigen group.¹⁴⁷

Condyloma Acuminata

Several studies reported favorable outcomes from isotretinoin treatment (0.5–1 mg/kg/day) in patients with condyloma acuminata that resist conventional therapy. High-dose oral isotretinoin (0.6 mg/kg/day) is more effective than low-dose (0.3 mg/kg/day) in treating cutaneous and genital warts, with 76% of patients achieving complete clearance compared to 46%.¹⁴⁸ Isotretinoin provides significantly better results than a placebo, and combination therapy was superior to isotretinoin monotherapy.⁸ An average of 96% of patients treated with isotretinoin combined with IFN alfa-n1 or IFN alfa-2a exhibited complete remission compared to 61.72% of those treated with isotretinoin monotherapy. Additionally, combination therapy decreased the treatment duration and the recurrence rate in this group of patients.^{149–153}

Evidence from RCTs of isotretinoin in condyloma acuminata treatment is summarized in Table 3.

Use of Oral Isotretinoin in Aesthetic Dermatology

Photoaging Skin

The most widely used treatments for photoaging skin are topical products, and evidence on the benefits of oral isotretinoin is still debated. The outcomes of aging skin following treatment with systemic isotretinoin remain mixed. Two RCTs demonstrated that 20 mg of isotretinoin daily does not significantly improve photoaging skin compared to topical retinoic acid or moisturizer/sunscreen by clinical, histology, and quality of life scores.^{156,157} Another two studies demonstrated a statistically significant increase in collagen fibers and overall skin improvement (wrinkle, skin texture, and coloration) in the treatment group with either 10 or 20 mg isotretinoin thrice weekly for three months.^{158,159} A literature review from 6 studies involving 251 patients

Table 3 Oral Isotretinoin and Its Uses in Condyloma Acuminata

Author and Year	Study	Number of Patients	Treatment Regimen	Results
Cardamakis et al 1995 ¹⁴⁹	Compare the efficacy of isotretinoin and isotretinoin with INFα-2a in condyloma acuminata	N=86	A. isotretinoin (1 mg/kg/day) for 3 months B. isotretinoin (1 mg/kg/day) with INFα-2a 3×10 ⁵ u subcutaneously 3/week until remission, but not more than 8 weeks	<ul style="list-style-type: none"> Lesion clearance in 26/42 of A and 40/44 of B Duration of therapy and recurrence rate significantly reduced in B
Georgala et al 2004 ¹⁵⁴	Compare the efficacy of oral isotretinoin and placebo in condyloma acuminata	N=53	A. isotretinoin (0.5 mg/kg/day) B. placebo • 12 weeks	<ul style="list-style-type: none"> Complete remission in 9/28 (32.1%) of A 8/9 remained in remission at 12 months
Reyna-Rodríguez IL et al 2021 ¹⁵⁵	Compare cryotherapy plus low-dose oral isotretinoin with cryotherapy alone for anogenital warts	N=46	A. isotretinoin 20 mg/day + cryotherapy B. cryotherapy • 6 weeks • Follow 4 months	<ul style="list-style-type: none"> A and B had 50% clearance Recurrence in A was not significantly lower than in group B (P = 0.59)
Nofal A et al 2022 ¹⁴⁸	Compare the efficacy between high versus low dose oral isotretinoin in cutaneous and genital warts	N=100	A. isotretinoin 0.6 mg/kg/day B. isotretinoin 0.3 mg/kg/day • Until remission but not more than 3 months	<ul style="list-style-type: none"> Complete clearance in 76% of A and 46% of B Recurrence was higher in B (26%) than in A (7.8%)

Abbreviation: INFα-2a, interferon alpha 2 a.

summarized that isotretinoin might be useful in treating photoaging, but there is currently insufficient evidence to support its use when weighing the potential risks.¹⁶⁰

Evidence from RCTs of isotretinoin in photoaging treatment is summarized in Table 4.

Sebaceous Hyperplasia (SGH)

SGH is characterized by enlarged sebaceous glands on the forehead or cheeks of middle-aged and older people causing unsightly and bothersome. Isotretinoin can reduce sebaceous gland size and inhibit sebum production.

According to one prospective study and eight case reports, it is possible to achieve complete or near-complete clearance of SGH by taking oral isotretinoin at a dosage of 0.14 to 1 mg/kg/day within 1 to 12 weeks.⁸ However, prior studies showed a high relapse rate in patients who do not receive consistent therapy.^{162,163} Several patients maintained their dosage of either isotretinoin 20 mg/day or 40 mg every other day to prevent relapse.^{164,165} To enhance the efficacy of treating SGH, isotretinoin can be used in conjunction with lasers and photodynamic therapy.¹⁶⁶

Table 4 Oral Isotretinoin and Its Uses in Photoaging

Author and Year	Study	Number of Patients	Treatment Regimen	Results
Hernández-Pérez et al 2000 ¹⁵⁸	Compare the improvement in cutaneous aging utilizing oral isotretinoin combined with different procedures of facial rejuvenation	N=120	A. isotretinoin (10–20 mg three times a week for 2 months) B. none	A significant difference was found in A (wrinkles, thickness of the skin, size of pores, skin elasticity, tone, mottled hyperpigmentation)
Rabello-Fonseca et al 2009 ¹⁵⁹	Compare the efficacy of different dosages of oral isotretinoin in clinical and histopathological evidence of photoaging	N=30	A. isotretinoin (10 mg three times a week) B. isotretinoin (20 mg three times a week) • 12 weeks	No significant differences between groups in increasing collagen fibers and improving texture, wrinkles depth, and skin coloration
Bagatin et al 2010 ¹⁵⁶	Compare the efficacy of oral isotretinoin and moisturizer/sunscreen in photoaging	N=32	A. isotretinoin (20 mg three times a week) B. moisturizer/sunscreen • 12 weeks	No significant differences between groups in epidermal thickness, number of collagen, and elastic fibers
Bagatin et al 2014 ¹⁵⁷	Compare the efficacy of low-dose oral isotretinoin and 0.05% retinoic cream in photoaging	N=24	A. isotretinoin (20mg/day) B. 0.05% retinoic cream • Every other day for 6 months	No significant differences between groups in the overall improvement of skin appearance and histology
Ianhez et al 2019 ¹⁶¹	Compare the efficacy of tretinoin 0.05% cream vs low-dose oral isotretinoin for the treatment of field cancerization	N=61	A. isotretinoin (10 mg/day) B. 0.05% tretinoin cream every other night • 6 months	No significant differences between groups in reducing the number of AKs, the thickness of stratum corneum, and the expression of p53 and Bax

Abbreviation: AKs, actinic keratoses.

Oily Skin (Hyper Seborrhea)

Face looking like an oily mess by noon and difficulty with makeup are problems in people with hyper seborrhea. Isotretinoin has been proven to be the highest reduction of sebum secretion among all treatment options for hyper seborrhea.

A prospective study revealed that sebum excretion rates were profoundly reduced after a 4-month course of isotretinoin at 1 mg/kg/day (79–83%) and remained significantly low one year following therapy (43–36%).¹⁶⁷ Even with a low dosage of isotretinoin (2.5–5mg/day), a reduction in sebum production of up to 64% can be observed. Additionally, biopsies have shown a 51% decrease in the size of sebaceous glands following a 6-month course of this therapy.¹⁶⁸ But a lower dose of isotretinoin is associated with a higher relapse rate of acne and hyper seborrhea.¹⁶⁹

Conclusion

Isotretinoin has increasingly been used to treat various dermatological conditions, in addition to its primary indication for severe acne vulgaris. Success stories of effectiveness in these conditions have expanded its potential usage beyond previously known. However, it is important to note that most studies are limited to case reports, case series, or prospective studies. Therefore, it is still necessary to conduct randomized controlled trials to confirm the effectiveness of isotretinoin in treating these conditions. When considering treatment options, carefully evaluating the potential benefits and drawbacks is crucial. For instance, it is important to consider the possible side effects of isotretinoin, especially for women of childbearing age.

Data Sharing Statement

Unavailable data, but the reader can personally request access via Dr. Anon Paichitrojjana; E-mail: anonpaic@gmail.com.

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