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REVIEW



# Oral isotretinoin for acne: a complete overview

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**ABSTRACT**

**Introduction:** Acne is one of the most common and widespread skin conditions, affecting the health as much as patients' quality of life. A wide variety of treatments for acne, topical and systemics, could be prescribed, depending on its degree of severity. Isotretinoin, a derivative of retinol, has been widely used for the treatment of severe forms of acne and those forms not responding to conventional treatments. In literature, there are several studies describing its efficacy, also reporting side-effects related to the drug; therefore, this has led the scientific community to request further studies qualifying its characteristics and comparing its efficacy and safety with other classic acne treatments, as well as with different treatment regimes, in order to find the dose with the best efficacy/safety ratio.

**Areas covered:** The aim of this article is to provide a complete overview on the use of oral isotretinoin for the treatment of acne describing the efficacy, safety, and tolerability of the drug.

**Expert opinion:** Oral isotretinoin represents a valid therapeutic alternative in treating severe and mild-to-moderate acne lesions, also reducing scarring damage. There are no standardized protocols regarding the use of oral isotretinoin and its association with other therapies; however, the correct patient selection and a tailored treatment protocol according to acne lesions severity and type should be considered in order to obtain optimal results.

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**KEYWORDS**
Isotretinoin; acne; treatment; acne scars; severe acne

## 1. Introduction

Acne is one of the most common and widespread skin conditions, affecting the health as much as patients' quality of life (QoL) [1,2]. Several factors are involved in the pathogenesis of acne, with hyperkeratinization of follicles, excessive sebum production, inflammation, and proliferation of Propionibacterium acnes being the most important ones. The majority of acne vulgaris can be classified as mild (85%); however, about 15% of affected patients develop the severe form of acne, which can result in various forms of scarring [3,4]. Treatment options for acne include topical treatments (retinoids and antibiotics), systemic medications (oral retinoids, antibiotics, and hormones), and non-pharmacological methods such as phototherapy. Topical treatments are mostly used for mild-to-moderate forms of acne, whereas severe forms of acne require systemic treatments with oral isotretinoin representing the most effective one [5,6]. Isotretinoin, a derivative of retinol (vitamin A), has been introduced in the early 1980s and has been widely used for the treatment of severe forms of acne and those forms not responding to conventional treatments. Although many studies describing its efficacy have been widely described, there are many articles reporting side-effects related to the drug; therefore, this has led the scientific community to request further studies qualifying its characteristics and comparing its efficacy and safety with other classic acne treatments, as well as with different treatment regimes, in order to find the dose with the best efficacy/safety ratio [7–9]. The objective of this review is to provide a complete overview on the use of oral isotretinoin for the treatment of acne vulgaris, used as single therapy or in association with other treatments.

## 2. Materials and methods

We searched for English-language literature regarding oral isotretinoin as treatment for acne in the following databases through 28 February 2022: PubMed, Embase, The Cochrane Library, Google Scholar, EBSCO, and Scopus. The following keywords were used: "acne", "isotretinoin", "oral isotretinoin", "severe acne", "scarring"; all terms are used in medical literature and were combined with the terms 'treatment,' 'therapy,' and 'acne.' All the published articles (case report, case series, prospective and retrospective studies, clinical trials, reviews, guidelines, and consensus) were reviewed to provide a complete overview of oral isotretinoin for acne. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

## 3. Pharmacokinetics and mechanism of action

Oral isotretinoin (13-cis retinoic acid) is a natural metabolite of vitamin A, approved for acne vulgaris in 1982 by the U.S. Food and Drug Administration (FDA) [7] and in 1983 by the European Medicines Agency (EMA) [8]. Being a highly

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**Article highlights**

- Acne is one of the most common skin conditions. A wide variety of treatments for acne, topical and systemics, could be prescribed
- Isotretinoin, a derivative of retinol, has been widely used for the treatment of severe forms of acne and those forms not responding to conventional treatments: it should be started at a dose of 0.5 mg/kg/day, increasing to 1 mg/kg/day, and continuing treatment until a dose of 120–150 mg/kg.
- As regard to different treatment regimens of oral isotretinoin, numerous studies have been conducted over the years. Several trials comparing the efficacy of oral isotretinoin used alone to the association of systemic, topical agents and physical treatment have also been conducted
- Although there are adverse reactions to the use of isotretinoin, the risk-benefit balance is in any case in favor of the administration of isotretinoin.
- Knowledge of the appropriate dose of the drug, periodic laboratory evaluation, the adoption of contraceptive methods in females and a correct lifestyle have positive effects on treatment process.

This box summarizes key points contained in the article.

lipophilic drug, its relative bioavailability increases if taken with food [9]. A novel formulation of isotretinoin, isotretinoin-lidose, uses lipid agents to incorporate lipophilic isotretinoin and can be taken before and after meals [10]. The drug is excreted to in feces and urines with the 13-cis-4-oxo-retinoic acid representing the main metabolite. In patients treated with isotretinoin at doses of 0.5–1 mg/kg/day, isotretinoin and its metabolites return to endogenous concentrations within 2 weeks after stopping treatment [11]. The efficacy of isotretinoin is due to its efficacy in reducing sebum production, normalizing follicular keratiniztion, thus inhibiting Cutibacterium acnes growth through a retinoic acid receptor mechanism, but also through [12] a retinoic acid receptor-independent mechanism that causes cell cycle arrest and apoptosis in sebocytes [13]. The induction of key genes as the tumor necrosis factor (TNF), FOX01 is linked to the apoptosis of sebocytes and keratinocytes suppression [14,15]. Furthermore, isotretinoin has also anti-inflammatory effects due to the reduction in monocyte Toll-like receptor-2 expression, the inhibition of neutrophil and monocyte chemotaxis [16] and the reduction of pro-matrix metalloproteinase (MMP)-9 and matrix metalloproteinase [17] in sebum. According to the European guidelines isotretinoin should be used in patients >12 years of age with severe papulopustular/moderate nodular acne and with severe nodular/conglobate acne that has or is not responding to systemic antibiotics and topical therapy [18]. Although the majority of clinical trials on acne treatment involve patients >12 years of age, there are severe cases in which the use of isotretinoin in patients aged <12 years could not be excluded [19,20].

According to the American Academy of Dermatology guidelines (2016) when treating patients with severe forms of acne, isotretinoin treatment in should be started at a dose of 0.5 mg/kg/day, increasing to 1 mg/kg/day, and continuing treatment until a dose of 120–150 mg/kg is achieved [21]. For patients with moderate acne, an inferior dose of 0.3–0.5 mg/kg/day is recommended. European guidelines (2016) recommend a dose of 0.3–0.5 mg/kg for severe papulo-pustular and moderate nodular forms of acne and a dose of >0.5 mg/kg for conglobate acne [21]. Conversely, a recent international consensus published by the Global Alliance to Improve Outcomes in Acne makes no specific recommendations regarding isotretinoin dosages but it simply recommends continuing isotretinoin until full clearance, plus an additional month, independent of cumulative dose [22]. Currently, there is no recommendation in relation to a specific cumulative dose. A systematic literature review [23] found that the cumulative dose target range was based on studies that were not designed to evaluate the role of cumulative dose on relapsing rates. Interestingly, no differences between patients who had taken a cumulative dose >120 mg/kg compared with patients taking <120 mg/kg have been described [24]. Borghi et al. [25] performed a prospective study including 150 patients with mild-to-moderate acne treated with isotretinoin until recovery and for 1 month thereafter. The mean cumulative dose was 81 mg/kg. The overall relapse rate was 9% in 2 years of follow-up and there was no statistically significant difference between relapse rates in patients with a cumulative dose of more than 120 mg/kg versus less than 120 mg/kg. Lately, a prospective study on 52 acne patients receiving a cumulative dose of above 120 mg/kg, showed no association between the cumulative dose and the risk of relapse [26].

## 4. Effectiveness of isotretinoin

The efficacy of oral isotretinoin in the treatment of moderate-to-severe acne has been studied since many years. However, new developments in dermatologist's therapeutic armamentarium have created the need for new clinical trials comparing the efficacy of isotretinoin used at different dosages or when associated with other systemic or topical treatments and even with physical treatments such as laser.

### *4.1. Isotretinoin: different treatment regimens compared*

As regards to different treatment regimens of oral isotretinoin, numerous studies have been conducted over the years [27,28]. Recently, Lee et al. [29] conducted a 24-week prospective study including 60 patients (40 female, 20 males; mean age: 22.26) randomly divided into three groups: (A) low daily dose (0.25–0.4 mg/kg/day); (B) conventional continuous dose (0.5–0.7 mg/kg/day); and (C) intermittent dose (1 week every 4). The global acne grading system (GAGS) score was used to assess improvement in acne severity, and the degree of satisfaction was evaluated on a four-point scale. At week 24, groups A and B reported equally efficacy and both were superior to group c in reducing inflammatory lesions.

Akman et al. [30] enrolled 66 patients with moderate-to-severe acne, randomly sorted into 3 groups given isotretinoin as follows: (A) 0.5 mg/kg/day for 6 months, (B) 0.5 mg/kg/day for 10 days per month for 6 months, and (C) 0.5 mg/kg/day for 1 month, followed by the same dosage for the first 10 days of each month for other 5 months. All groups showed the same reduction in acne severity, but the incidence of recurrence at 12-month follow-up period was higher for groups B and

C than for group A. Another treatment regimen was tested by Ahmad et al. [31] which compared single or double administration of isotretinoin over a period of 22 weeks reporting no statistical significant difference.

Agarwal et al. [32] enrolled 120 patients with acne from mild-to-severe assessed by Definition Severity Index, have demonstrated faster clearance of lesions with isotretinoin 1 mg/kg/day than with other treatment protocols (see Table 1 for details). The authors therefore recommend an initial full-dose for 8 weeks followed by a low-dose regimen for the other weeks due to the fewer related side-effects. Later, Borghi et al. [25] also confirmed that a low-dose regimen of oral isotretinoin is superior to the conventional full dose in mild-to-moderate forms of acne. On the other hand, Boyraz and Mustak [33], compared the efficacy of intermittent (0.5–0.75 mg/kg per day for 1 week per month) and continuous low-dose (20 mg/kg/day) regimens of isotretinoin in moderate acne for 6–8 months (see Table 1 for details). The low-dose continuous regimen proved to be slightly superior due to both greater compliance and lower risk of recurrence. Low-dose isotretinoin (5 mg/day) was demonstrated to be effective also after 4 weeks of treatment [34] in mild form of acne, whereas, different trials showed low-dose isotretinoin (20 mg/day) to be effective after 3 months of treatment in patients with moderate-to-severe forms of acne [35,36]. Interestingly, there were no differences in clinical efficacy regarding the different isotretinoin formulations, even though the food-independent pharmacokinetics type was the most preferred [37–40].

### 4.2. Isotretinoin vs isotretinoin in association with other systemic treatments

Several studies evaluated the clinical efficacy of isotretinoin in combination with other systemic treatments; Pandey and Agrawal [41] conducted a 12-week prospective study involving 100 patients with severe acne to compare the efficacy and safety of isotretinoin in association with levocetirizine with isotretinoin alone. The authors found better clinical response in the combined treatment group, with a lower rate of flaring up and fewer adverse events due to the synergistic effect of levocetirizine.

Studies comparing isotretinoin to isotretinoin and oral antibiotics association were also conducted. In particular, De and Kanwar [42] enrolled 66 patients with severe acne (40 males; mean age 20.4) treated with a combination of low-dose isotretinoin (0.3 mg/kg/day) and pulsed oral azithromycin (500 mg/day for 3 days every 2 weeks) for 16 weeks. The mean total cumulative dose of isotretinoin was 49.6 mg/kg, and 93.9% patients reached complete regression of the disease. Similar results were also described in other studies [43].

### 4.3. Isotretinoin vs oral antibiotics and/or topical agents

Several trials comparing the efficacy of oral isotretinoin used alone to the association of antibiotics and topical agents have also been conducted; in a randomized controlled trial, involving 60 patients with moderate-to-severe acne (aged from 15 to 30 years), Wahab et al. [44] compared the efficacy of isotretinoin 0.5–1 mg/kg (group A) to oral azithromycin at a dose of 500 mg 3 days a week for 3 weeks (group B); overall, only 16.7% of patients in group A had a relapse of the disease vs 33.3% in group B. Moreover, the cure rate reported was 100% and 80% in groups A and B, respectively.

Gollnick et al. [45] enrolled 85 males with severe acne to test the efficacy of minocycline plus azelaic acid (AA) combination (A) vs isotretinoin (B) (see Table 1 for details). Results at 6 months were as follows: mean reduction of comedones: 70% (A) vs 83% (B), of papules and pustules: 88% (A) vs 97% (B), of deep inflammatory lesions: 100% (A) vs 100% (B). The authors therefore considered AA plus minocycline to be a valid alternative in cases of contraindication to isotretinoin or as maintenance therapy.

In contrast, better results were reported in patients with moderate-to-severe acne when treated with oral tetracyclines combined with adapalene [46]. A large cohort study [47] involving 266 patients, compared the efficacy of 200 mg oral doxycline associated with topical adapalene 0.1%/benzoyl peroxide 2.5% (D + A/BPO) gel versus oral isotretinoin (see Table 1 for details). Isotretinoin resulted to be superior to D + A/BPO in reducing nodules (95.6% vs 88.7%), papules/pustules (95.2% vs 79.6%), comedones (92.3% vs 75.9%) and total lesions (92.9% vs 78.2%, $p < 0.01$), respectively.

Dhir et al. [48] conducted a comparative study between isotretinoin 20 mg twice daily plus topical clindamycin 1% and adapalene 0.1% for 24 weeks vs isotretinoin 20 mg twice daily for 24 weeks.

At week 24 there was a complete, excellent or good response in 100% of the isotretinoin group and 92% of the combined treatment group. No significant difference was reported between the two groups. Oral isotretinoin showed to be superior when associated with topical treatment as dapsone 5% gel [49] or clindamycin 1% gel [50].

However, it should be emphasized that isotretinoin takes up to 2–3 months to induce the first improvements, whereas the other treatment options examined induce a more rapid improvement, and not all the studies examined include a follow-up period so that possible relapses cannot be assessed. In addition, a limitation of antibiotic therapy is the need for multiple courses, which often leads to poor compliance and hence the development of scars.

### 4.4. Isotretinoin vs isotretinoin in association with physical treatment

In recent years, different studies have explored the efficacy of isotretinoin in association with physical treatments such as lasers. In particular, Xia et al. [51] investigated a combined treatment of 1,550-nm NAFL with low-dose isotretinoin (10 mg/day) in a population of 24 Asians with moderate-to-severe acne. Each individual patient had treatment on a single half-face (side A), while the other half acted as a control (side B) and received 30–45 days of low-dose isotretinoin before starting laser treatment. The protocol included one laser session (low-energy mode 20 mJ/cm$^2$ and 100–169 points per area) per month for 3 months. At the end of the 3 sessions both sides showed a significant improvement (mean Leeds acne-grading scores decreased from 10.6 to 5.8 on side B and from 10.4 to 3.5 on side A, with

Table 1. Clinical trials reporting the efficacy of oral isotretinoin alone or in association with other treatments.

| Study | Objectives | Population | Dosage | Follow-up | Ref |
|---|---|---|---|---|---|
| Randomized controlled-single center study | Clinical efficacy and tolerability of low dose and intermittent isotretinoin regimens compared to conventional isotretinoin treatment | 60 patients with moderate acne (20 male) | Isotretinoin 0.25–0.4 mg/kg/day (group A)<br>Isotretinoin 0.5–0.7 mg/kg/day (group B)<br>Isotretinoin 0.5–0.7 mg/kg/day for 1 week every 4 (group C) | Week 24 | Lee et al [29] |
| Randomized controlled-multicenter study | Clinical efficacy and tolerability of low dose and intermittent isotretinoin regimens compared to conventional isotretinoin treatment | 66 patients with moderate-to-severe acne (23 male) | Isotretinoin 0.5 mg/kg/day for 6 months (group A)<br>Isotretinoin 0.5 mg/kg/day for 10 days per month for 6 months (group B)<br>Isotretinoin 0.5 mg/kg/day for one month, followed by the same dosage for the first 10 day of each month for other 5 months (group C) | Week 2, 4, 8, 12, 16, 20, 24 during therapy; then every 3 months for 12-month post-treatment follow-up | Akman et al [30] |
| Randomized controlled-single center study | Clinical efficacy, tolerability and laboratory changes during isotretinoin therapy full dose or divided dose daily | 58 patients with acne from mild to very severe (15 male) | Isotretinoin 0.5–1 mg/kg/day full dose once daily (group A)<br>Isotretinoin 0.5–1 mg/kg/day twice daily divided dose (group B) | Week 22 | Ahmad et al [31] |
| Randomized controlled-single center study | Clinical efficacy and tolerability of isotretinoin in daily, alternate, pulse and low-dose regimens | 120 patients with acne from mild to severe (66 male) | Isotretinoin 1 mg/kg/day (group A)<br>Isotretinoin 1 mg/kg alternate day (group B)<br>Isotretinoin 1 mg/kg/day for 1 week every 4 (group C)<br>Isotretinoin 20 mg every alternate day for 16 weeks (group D)<br>* In addition to isotretinoin, patients also received azithromycin 500 mg 3 days a week for 3 weeks and applied clindamycin 1% gel twice daily | Week 8, 16 | Agarwal et al [32] |
| Open, prospective, non-comparative study | Clinical efficacy of an isotretinoin-sparing protocol | 150 patients with mild-to-moderate acne | Initial Isotretinoin dose ≤0.2 mg/kg, than the dosage was increased by 5 mg every 2 weeks, until the highest dose tolerated was reached | Every 3 months during the 2-year follow-up period | Borghi et al [25] |
| Randomized controlled-single center study | Clinical efficacy of intermittent and continuous low-dose isotretinoin regimens | 60 patients with moderate acne (24 male) | Isotretinoin 0.5–0.75 mg/kg/day for 1 week per month (group A)<br>Isotretinoin 20 mg/kg/day (group B) | 6 months | Boyraz and Mustak [33] |
| Randomized placebo-controlled study | Clinical efficacy of 5 mg/day isotretinoin | 58 patients with low-grade acne (26 male) | Isotretinoin 5 mg/day for 32 weeks (group A)<br>Placebo for 16 weeks, followed by open-label 5 mg/day of isotretinoin for the next 16 weeks (group B) | Week 32, than further 10 weeks off treatment | Rademaker et al [34] |
| Prospective non-comparative study | Clinical efficacy and tolerability of low-dose regimen | 50 patients with moderate-to-severe acne (38 male) | Isotretinoin 20 mg/day for 3 months | 6 months | Rao et al [35] |
| Prospective non-comparative study | Clinical efficacy of low-dose regimen | 638 patients with moderate acne | Isotretinoin 20 mg/day for 6 months | Every 2 months during therapy, then 4-year post-treatment follow-up | Amichai et al [36] |
| Randomized controlled-multicenter study | Clinical equivalence between micronized and standard isotretinoin | 602 patients with severe acne (315 male) | 0.32–0.4 mg/kg/day of micronized isotretinoin once daily without food (group A)<br>0.85–1.18 mg/kg/day of standard isotretinoin into two divided doses with food (group B) | Week 20 | Strauss et al [37] |
| Randomized controlled-multicenter study | Compare safety profiles of isotretinoin-Lidose and standard isotretinoin | 925 patients with severe recalcitrant nodular acne | 1 mg/kg/day of isotretinoin-Lidose for 20 weeks (group A)<br>0.5 mg/kg/day first 8 weeks, then 1 mg/kg/day until week 20 of standard isotretinoin (group B) | Week 20 | Webster et al [38] |
| Open-label, single-arm, multicenter Phase IV study | Evaluation of long-term relapse rates following lidose-isotretinoin | 201 patients with severe recalcitrant acne (125 male) | Initial dosage of isotretinoin 0.5 mg/kg/day for 4 weeks, followed by 1 mg/kg/day for 16 weeks | Every 2 weeks in the first month, then every 4 weeks. 104 weeks post-treatment follow-up | Del Rosso et al [39] |
| Open-label multicenter study | Impact on quality of life of Lidose-isotretinoin | 197 patients with severe recalcitrant acne (125 male) | Initial dose of isotretinoin 0.5 mg/kg/day for 4 weeks, followed by 1 mg/kg/day for 16 weeks | Week 2, 4, 8, 12, 16 and 20 | Zaenglein et al [40] |

(*Continued*)

Table 1. (Continued).

| Study | Objectives | Population | Dosage | Follow-up | Ref |
|---|---|---|---|---|---|
| Prospective study | Clinical efficacy and safety of combining isotretinoin and antihistamine vs isotretinoin alone | 100 patients with moderate-to-severe acne | N/A | Week 4, 8, 12 | Pandey et al [41] |
| Open-label prospective non-comparative single-center study | Clinical efficacy of antibacterial combinated with low-dose isotretinoin | 66 patients with severe acne (40 male) | Isotretinoin 0.3 mg/kg/day and pulsed oral azithromycin (500 mg/day over 3 consecutive days every 2 weeks) until complete clinical clearance or to week 16 | Every month, then follow-up for 1 year after complete clearance of disease | De et al [42] |
| Open-label non-comparative study | Clinical efficacy of antibacterial combinated with low-dose isotretinoin | 82 patients with moderate-to-severe acne | Isotretinoin 0.3 mg/kg/day plus pulsed oral azithromycin (500 mg/day for 3 consecutive days per week for one month) | Week 24 | Hasibur and Meraj [43] |
| Randomized controlled-single center study | Compare efficacy of isotretinoin and antibacterial | 60 patients with moderate-to-severe acne (33 male) | Isotretinoin 0.5–1 mg/kg for 5 months (group A)<br>Azithromycin 500 mg 3 days a week for 3 months (group B) | N/A | Wahab et al [44] |
| Randomized controlled-multicenter study | Compare efficacy of minocycline plus azelaic acid vs isotretinoin | 85 patients with severe acne (85 male) | 20% azelaic acid cream twice daily plus oral minocycline 50 mg twice daily, followed by 3 months of maintenance with 20% azelaic acid cream twice daily (group A)<br>Isotretinoin 0.8 mg/kg in the first month, 0.7 mg/kg in the second month, 0.5–0.7 mg/kg in the third month, 0.5 mg/kg in the fourth-sixth months, with the following 3 months without therapy (group B) | 6 Months | Gollnick et al [45] |
| Randomize controlled-single center study | Compare efficacy of topical tetracyclines plus adapalene vs isotretinoin | 49 patients with moderate-to-severe acne (32 male) | Tetracycline hydrlocloride 500 mg twice daily plus topical adapalene once daily for 24 weeks (group A)<br>Isotretinoin 1 mg/kg/day, divided into two doses, for 24 weeks (group B) | Months 2, 4, 6 during treatment, then month 2 in post-treatment follow-up | Oprica et al [46] |
| Randomized controlled-multicenter study | Compare efficacy of oral doxycline plus adapalene/benzoyl peroxide gel vs isotretinoin | 266 patients with severe acne (127 male) | Doxycline 200 mg plus adapalene 0.1%/benzoyl peroxide 2.5% gel once daily for 20 weeks (group A)<br>Isotretinoin once daily (0.5 mg/kg/day for the first 4 weeks, then 1 mg/kg/day for the following 16 weeks, with a mean cumulative dose of 136 mg/kg) (group B) | Week 2, 4, 8, 12, 16, 20 | Tan et al [47] |
| Randomized controlled-single center study | Compare efficacy of isotretinoin plus topical clindamycin 1% and adapalene 0.1% vs isotretinoin twice daily alone | 60 patients with severe acne (44 male) | Oral isotretinoin 20 mg twice a day along with topical clindamycin (1%) during the daytime and adapalene (0.1%) at bedtime for 24 weeks (group A)<br>Oral isotretinoin 20 mg twice a day for 24 weeks (group B) | Week 24 | Dhir et al [48] |
| Randomized placebo-controlled study | Compare efficacy of isotretinoin alone vs isotretinoin plus dapsone gel 5% | 58 patients with moderate-to-severe acne (25 male) | Isotretinoin 20 mg once daily plus placebo gel (group A)<br>Isotretinoin 20 mg once daily plus dapsone 5% twice daily (group B) | Week 8 | Faghihi et al [49] |
| Open prospective non-comparative study | Clinical efficacy of clindamycin gel 1% plus isotretinoin at low dose | 305 patients with moderate-to-severe acne (107 male) | Isotretinoin 20 mg every alternate day for 6 months along with topical clindamycin gel 1% | Every 1 month until month 6 | Sardana et al [50] |
| Randomized controlled-single center study | Clinical efficacy and safety of Nonablative fractional laser treatment combinated with low-dose oral isotretinoin | 24 patients with moderate-to-severe acne | Each individual patient had treatment on a single half-face (side A), while the other half acted as a control (side B) and received 30–45 days of low-dose isotretinoin before starting laser treatment. The protocol included one laser session (low-energy mode 20 mJ/cm$^2$ and 100–169 points per area) per month for three months | Every month during treatment, then every 3 months in post-treatment follow-up | Xia et al [51] |

(*Continued*)

Table 1. (Continued).

| Study | Objectives | Population | Dosage | Follow-up | Ref |
|---|---|---|---|---|---|
| Randomized controlled-single center study | Clinical efficacy, safety and satisfaction of isotretinoin combinated with 420 nm intense pulsed light | 47 patients with moderate-to-severe acne | Isotretinoin 0.5–0.75 mg/kg/day for 8 weeks (group A) isotretinoin for 8 weeks co-administered with 420 nm intense pulsed light (spot size 10 mm x 20 mm, pulse duration 30 ms or 40 ms, and fluence 10–15 J/cm$^2$) twice weekly for 4 weeks (group B) *Both groups topically applied adapalene 0.1% gel and fusidic acid 2% cream once daily | Week 12, then at month 2 in post-treatment follow-up | Li et al [52] |

a significant difference ($p < 0.05$)). All acne lesions improved more on the A side than on the B, including boxcar atrophic scars, but not icepick or rolling scars. In conclusion, isotretinoin effectively controls nodules, papules, and pustules, while 1,550-nm Er:glass NAFL significantly reduces the number of comedones and atrophic boxcar scars. Their combination has an excellent efficacy/safety ratio in moderate-to-severe acne. Moreover, Li et al. [52] evaluated oral isotretinoin when associated with 420 nm intense pulsed light (IPL) (see Table 1 for details). The combined treatment group (B) experienced a significant decrease in GEA grade compared to the control group with isotretinoin alone (A) ($p < 0.05$). There was also a significant decrease in the number of inflammatory lesions (56.5% vs 79.2% A vs B group) but not in the number of non-inflammatory lesions (52.2% vs 56.5% A vs B group). The combined treatment of low-dose isotretinoin plus 420 nm IPL was therefore statistically and clinically effective, with the advantage of limited duration.

## 5. Adverse events

Adverse events occurring during isotretinoin treatment could be divided into cutaneous and extracutaneous ones.

### 5.1. Cutaneous adverse reaction

Dryness and desquamation of the skin and mucous membranes are common side effects: above all, cheilitis (90–100% of individuals) is the most common mucocutaneous adverse event [53]. They develop as a result of a pharmacologically induced sebum-suppressive effect [54], thickness of stratum corneum and alteration of cutaneous barrier [55,56], which cause xerotic and desquamative alterations; these adverse events mainly involve sites with a high concentration of sebaceous glands such as face, chest, and back. They are reversible, dose-dependent, predictable, and manageable. The absence of these reactions raises the possibility of underdosing [57]. On the contrary, when patients are given a dose that is too high for them, they may experience dryness of nose and eyes. Another uncommon reaction that can occur when the dose of isotretinoin is too high is acne fulminans [58]. Other severe skin reactions (e.g. Stevens–Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis) have only been observed in few occasions [59].

### 5.2. Extracutaneous adverse reaction

The most serious side effect is teratogenicity. The overexpression of the proapoptotic transcriptional gene p53, which causes apoptosis in neural crest cells, is considered the main hypothesis [14,60]. A pregnancy test before beginning therapy and monthly thereafter must be required, as the use of safe contraceptive methods during and for 1 month after stopping the therapy. In a high percentage of cases (65–85%), the pregnancy proceeds without problems. The risk of spontaneous abortion is estimated between 10.9% and 20%, while the risk of birth defects, which includes craniofacial, thymus, and cardio anomalies, is 18–28% [61]. Isotretinoin treatment has also been associated with depression; their relationship still remains controversial. Depressive symptoms in patients treated with isotretinoin were first reported in 1983 [62]. The US FDA issued a warning in 1998 about the possibility for isotretinoin to cause depression, psychosis, suicidal ideation, and suicide. For patients receiving isotretinoin, the FDA recommends the use of signed informed consent forms and a printed patient medication guide [63–65].

A meta-analysis published in 2017 screened 172 studies: among them, only 31 met the inclusion criteria and were subjected to analysis. Of the 31 studies, only one population-based study found that isotretinoin significantly increased the risk of depression. This meta-analysis found no association between isotretinoin and depression. Furthermore, symptoms of depression improved after treatment with isotretinoin, but this effect was not significantly different from the improvement experienced by patients that were prescribed alternative therapies [66].

In addition, a recent meta-analysis, published in 2019 from the same authors, analyzing 17 studies, confirmed the association between the use of isotretinoin with depression symptoms improvement and the absence of association between the use of isotretinoin and the risk of depressive disorders. This association was statistically significant only on pooling retrospective studies, but it was not evident on pooling prospective studies [67].

Suarez et al. found that depression is linked to acne independently from the use of isotretinoin [68]. Therefore, it is the physician's responsibility to assess the risk of depression in all acne patients regardless of the treatment prescribed. Probably some patients are more susceptible to depression [69] and the hypothesis of an idiosyncratic reaction cannot be ruled out [70]. Isotretinoin has also been linked to ocular changes,

mostly in the ocular surface. Dry eye disease (DED), blepharoconjunctivitis, abnormal meibomian gland secretion or atrophy, chalazion or hordeolum are common adverse events reported. Other reactions, like photophobia, corneal opacities, keratitis, refractive change, impaired night vision/decreased color vision, papilledema are rarer [71].

Furthermore, isotretinoin use has been associated to neuro-ophthalmological abnormalities, worsened dark adaption and color vision, cataract, retinal toxicity such as serous retinal detachment, premacular hemorrhage, vascular occlusions, and vitreous abnormality [72–76]. They are associated with a variety of symptoms including eye discomfort, dryness, foreign body sensation, pain, photophobia, blurred vision, red and watery eyes (as reflex tearing). It is also common for patients to report worsening of symptoms in windy, dry or air-conditioned locations [59,77–79]. Isotretinoin use has also been linked to blepharonconjunctivitis, an inflammation of the eyelids and conjunctiva [80]. It is possible to prevent the onset of these alterations by changing lifestyle: reducing exposure to wind, dry environments, and air conditioning can help reduce patient discomfort [81]. Even the use of medium and high viscosity artificial tears can improve symptoms [82,83]. Musculoskeletal side effects, such as arthralgia, myalgia, back pain, spondyloarthropathy-related symptoms, and sacroiliitis have been described in patients undergoing isotretinoin treatment. Low back pain is one of the very common complications of isotretinoin. It can have both mechanical and inflammatory pathogenesis. Specialists should be aware that back pain can be a symptom of sacroiliitis during use of isotretinoin and that it is dose related. Although sacroiliitis is an uncommon isotretinoin side effect, inflammatory back pain without sacroiliitis is common [84]. Other uncommon musculoskeletal disorders related with isotretinoin are arthritis, enthesitis, hyperostosis and extraspinal calcifications (these two mainly affect the cervical vertebrae), costochondritis, osteoporosis, growth retardation, premature epiphyseal closure in children and as well as gout [85–88]. Furthermore, calcification on tendons and ligaments were commonly reported [89,90]. More than one case of gastrointestinal alterations concomitant or subsequent to the intake of isotretinoin have been described in literature; several studies have been conducted to demonstrate the possible association between gastrointestinal diseases, such as Crohn's disease and celiac disease, in patients receiving isotretinoin. A population-based cross-sectional study published by Benjamin Lebwohl et al. [91] found no link between isotretinoin use and celiac disease, but a modest increased risk of celiac disease in people with an acne diagnosis [92]. A recent retrospective cohort analysis studied the incidence of IBD among patients with acne vulgaris with and without isotretinoin exposure showing that IBD incidence among isotretinoin-exposed patients with acne is very low, and the risk is almost the same to unexposed acne patients [93]. On the other hand, a case-control study from the Mayo Clinic suggests a protective role for isotretinoin against IBD, as it was found to have a reduced risk in the test population, although the population consisted of a small number of IBD cases [94].

## 6. Laboratory evaluation

Lipids and hepatic enzymes, at baseline and at month 1 and 3 thereafter must be evaluated when using isotretinoin [8]. Published guidelines do not give detailed recommendations on laboratory monitoring during isotretinoin therapy [95–97]. Alteration of lipids, liver enzymes, and blood counts during isotretinoin treatment are the values more often alterated [98]; moreover, changes in white blood cells have also been described. A cohort study of 1863 patients receiving isotretinoin for acne between January 2008 and June 30, 2017 reported severe laboratory abnormalities of triglyceride and liver function in fewer than 1% and 0.5% of the patients, respectively. No severe cholesterol or complete blood count abnormalities were observed. The authors suggested reducing the frequency of lipid and liver function monitoring and to eliminate complete blood count monitoring [99]. In a cohort of 515 patients receiving oral isotretinoin, 2.4% presented leukopenia, 1,6% non-significant thrombocytopenia, and 3,3% increased level of alanine aminotransferase [100] concluding that routine testing is not recommended, unless there is a known hematologic disorder or risk factor. Recent series has helped to standardize laboratory monitoring. For patients starting isotretionoin, it is recommended to dose liver function tests and lipid profile at baseline and after 2 months. Further testing may be considered if fasting values are significantly abnormal or their medical or family history indicates a higher risk [58]. The importance of noting triglyceride elevation during the treatment course is due to increased atherosclerosis risk which remains after stopping treatment later in life; moreover, there is a risk, extremely rare, of hypertriglyceride-induced pancreatitis [101]. For these reasons, prolonged use of isotretinoin in patients with underlying lipid disorders is not recommended [102]. When triglycerides are elevated, it can be helpful to repeat the test and be certain the patient was fasting. For moderate elevations (300–500 mg/dL) of triglycerides, recommendations include weight reduction, increased physical activity, and a low-fat, low-carbohydrate, low-alcohol diet. Omega-3 fatty acid integration may be useful to manage high triglyceride levels in patients taking isotretinoin, especially those with elevated triglyceride levels at baseline [103–106]. When triglyceride levels are over 500 mg/dL, the isotretinoin dose can be decreased, in addition to the lifestyle and diet changes previously mentioned. If the triglyceride levels remain elevated, treatment with a lipid-lowering agent may be required (such as a fibric acid derivative, niacin, or statin). Triglyceride elevations >800 to 1000 mg/dL can cause pancreatitis and isotretinoin may need to be stopped until lipids are better managed. Lipid elevations are reversible upon cessation of isotretinoin [107]. Liver function tests traditionally often refer to ALT and AST that are also present in muscle tissue and correlate more with creatine kinase (CK) levels. γ-Glutamyltransferase (GGT) may be more specific for liver injury during isotretinoin therapy. Serum CK level dosage can be considered, especially in physically active patients. Some experts recommend checking baseline CK levels in all patients, and regular monitoring in those with baseline abnormalities and/or patients who have CK levels approaching or exceeding five times the normal value may discontinue or reduce

physical activity or isotretinoin dosage until CK level normalization [108].

Due to isotretinoin teratogenic effect, female patients have to present a negative serum pregnancy test within 3 days before first prescription and every month during treatment and for at least 1 month after the end of treatment [8]. In addition, in the USA the strict pregnancy prevention program iPLEDGE is mandatory [18]. The iPledge program, currently in place in the US, was established in 2006 and requires women of childbearing potential to abstain or to commit to using two forms of contraception for all the duration of therapy and for at least 30 days after the end of the isotretinoin treatment. Patients must have two negative pregnancy tests 1 month apart before starting isotretinoin, and monthly thereafter [109].

## 7. Predictive markers of therapeutic response

Preneau et al. conducted a study including 32 women with acne vulgaris of face and trunk treated with isotretinoin (0.5 mg/kg) over a 6-month period [110]. A significant relationship was also found between the therapeutic response on the face and the high-glycemic-load diet and high BMI: patients with a high glycemic-load diet had a lower therapeutic response on the face. Moreover, the therapeutic response was higher when the BMI was low. So, low glycemic-load diet and low BMI could be considered predictive markers of response to isotretinoin in female acne patients, but other studies are needed to estabilish the correlation.

## 8. Expert opinion

Acne vulgaris is a common inflammatory skin disorder mostly affecting young patients and highly impacting on their quality of life. It sometimes represents a risk factor for depression, anxiety and in severe cases, even suicides [1–3,111]. A wide variety of topical and systemic treatments do exist with oral isotretinoin being one of the most common and effective one. A prompt treatment, reducing inflammation, in particular for moderate-to-severe forms of acne should be always considered in order to avoid permanent consequences as scarring and pigmentary changes [111]. Oral isotretinoin represents a valid and cost-effective therapeutic alternative in treating severe and mild-to-moderate acne lesions, also reducing scarring damage [5]. Oral isotretinoin has been used for the treatment of acne for more than 40 years, and no serious side-effects have ever been reported to cause discontinuation, proving its safety and efficacy. It is currently the only drug that can cure acne and maintain the result with even a single cycle, provided that the protocol is followed properly, i.e. until complete remission of the symptoms plus a further month thereafter. In fact, recurrence occurs when the lesions are still in an inflammatory phase, as long as the recommended cumulative dose is not exceeded. As reported in our review, new effective oral isotretinoin formulations and new dosing regimens, including low-dose isotretinoin (0.1–0.3 mg/kg daily) or intermittent protocols have been proposed in order to reduce dose-dependent drug-related adverse events, avoiding treatment discontinuation [6]. Knowledge of the appropriate dose of the drug, periodic laboratory evaluation, the adoption of contraceptive methods in females, and a correct lifestyle have positive effects on treatment process. To date, several studies have also demonstrated the objective efficacy of isotretinoin in reducing acne severity grading when used in association with other topical or systemic treatments. A synergistic effect has been also described for the association of oral isotretinoin with physical treatments, such as laser therapy, in improving acne scars lesions; in our clinical practice, oral isotretinoin has been widely used alone, only associated with topical products as hydrants and antibiotic creams. The superiority of synergistic effect and is demonstrated by the rapidity and degree of improvement, the reduction of the recovery time, and the higher patients' grade of satisfaction compared to the treatment used alone. There are no standardized protocols regarding the use of oral isotretinoin and its association with other therapies; however, the correct patient selection and a tailored treatment protocol with a specific planning of treatment sessions according to acne lesions severity and type should be considered in order to obtain optimal results.

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## Author contribution

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