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Review

Isotretinoin and Hepatotoxicity in Patients with Acne: A Narrative Review

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Abstract: Acne vulgaris is a prevalent dermatological condition that is often treated with isotretinoin, a potent medication effective in moderate to severe cases. However, its use requires careful monitoring because of its potential hepatotoxic effects. Isotretinoin has been associated with transient elevations in liver enzyme levels, with mild abnormalities observed in up to 11% of cases. Severe elevations (grade $\geq$ 3), indicating potential liver dysfunction, occur infrequently, with an incidence of approximately 0.2% to 0.5%. The mechanisms underlying isotretinoin-induced liver injury involve oxidative stress and genetic susceptibility, primarily manifesting as idiosyncratic drug-induced liver injury. Most enzyme abnormalities occur within the initial months of treatment, and their clinical significance varies, with many cases resolving without intervention. A review of large cohort studies highlighted the incidence of abnormal liver function tests, including elevated alanine aminotransferase and aspartate aminotransferase levels. These abnormalities are often present within the first 3 months of therapy, particularly at higher cumulative doses. The role of routine liver function monitoring is debated, with recommendations favoring baseline and early follow-up tests and further testing guided by clinical indicators. Alanine aminotransferase may serve as a more specific marker for liver injury compared to other markers, such as aspartate aminotransferase. This review highlights the importance of evidence-based guidelines to balance effective acne treatment with the risk of isotretinoin-induced hepatotoxicity. Standardizing monitoring protocols and integrating genetic and oxidative stress markers may enhance safety and therapeutic outcomes. Further research is essential to refine these strategies and address gaps in long-term hepatotoxicity data.

Keywords: isotretinoin; hepatotoxicity; acne vulgaris; liver function tests; drug-induced liver injury; retinoids

Academic Editor: Nikolaos Labrou

Received: 18 December 2024
Revised: 16 January 2025
Accepted: 21 January 2025
Published: 22 January 2025

Citation: Tawanwongsri, W.; Kanchanasuwan, T.; Eden, C. Isotretinoin and Hepatotoxicity in Patients with Acne: A Narrative Review. *Cosmetics* **2025**, *12*, 17. https://doi.org/10.3390/cosmetics12010017

1. Introduction

Acne vulgaris is one of the most prevalent dermatological conditions, affecting approximately 20.5% of the global population. The disorder exhibits a peak incidence among individuals aged 16–24 years, with a prevalence rate of 28.3%. The distribution of acne varies across geographical regions, demonstrating a higher prevalence in East Asia, Latin America, and the Middle East; a lower prevalence in Europe and Australia; and no significant variations in Africa [1]. While it usually begins in the teenage years, this dermatological issue can extend into adulthood and shows an increasing trend among adult women [2].

Both internal and external exposure factors influence acne [3]. Strong associations have been observed between the presentation or severity of acne and factors, such as family history, age, body mass index, and skin type. By contrast, the links between acne and other factors such as diet and smoking, remain inconsistent [4]. The pathophysiology of acne is driven by four primary factors: increased sebum production, follicular hyperkeratinization, colonization by *Cutibacterium acnes*, and inflammation [5]. Isotretinoin effectively targets all of these factors, making it a comprehensive treatment option. However, its use requires adherence to specific indications and careful monitoring because of its potential for significant side effects [6,7]. It is considered a treatment option for individuals with moderate-to-severe acne, where moderate acne is characterized by numerous non-inflammatory lesions with some inflammatory lesions and no more than one small nodule, whereas severe acne involves numerous non-inflammatory and inflammatory lesions, including multiple nodules [8,9].

Despite its indication for at least moderate severity, isotretinoin has increasingly been used off-label to treat mild to moderate cases that are unresponsive to topical or other oral therapies or those that relapse quickly after discontinuation of oral antibiotics [10]. Adelman et al. reported that among 4605 men eligible for isotretinoin treatment in this population, 988 (21.5%) received a course of medication [11]. Men were more likely to receive isotretinoin than women (odds ratio: 2.34, 95% confidence interval [CI]: 2.13–2.57). However, Sa et al. reported a high prescription rate, with the prevalence of isotretinoin use reaching 57.61% [12]. The standard dosing regimen for isotretinoin typically ranges from 0.5 to 1.0 mg/kg/d, aiming for a cumulative dose of 120 to 150 mg/kg [13]. This dose range is based on a balance between efficacy and safety. As a lipophilic drug, isotretinoin accumulates in fatty tissues, resulting in a high volume of distribution [14]. Dosing isotretinoin based on total body weight (TBW) ensures an accurate reflection of the increased volume of distribution in obese patients, facilitates proper drug redistribution, and maintains therapeutic efficacy [15]. This approach aligns with the recommendations in the U.S. Food and Drug Administration (FDA)-approved patient medication guides [16,17]. Khismatulina et al. found that daily isotretinoin doses of 0.5, 0.7, or 1.0 mg/kg, with a cumulative dose of 120 mg/kg, were administered over an 18-month observation period [18]. Faster resolution of inflammatory lesions was observed at doses of 0.7 mg/kg and 1.0 mg/kg ($p < 0.001$). Relapse rates during the 18-week follow-up were 18.75% for the 0.5 mg/kg dose, 12.5% for the 0.7 mg/kg dose, and 3.2% for the 1.0 mg/kg dose, showing significant differences ($p = 0.003$). In very severe cases, daily doses may be increased to 1.3–2.0 mg/kg, with cumulative doses reaching up to 290 mg/kg [19]. For mild to moderate acne, lower doses of 0.1 to 0.4 mg/kg/day over a treatment period of 6 to 8 months have been shown to be effective [20,21]. The most frequent side effects of isotretinoin treatment are in the mucocutaneous, musculoskeletal, and ophthalmic systems [9]. Higher doses are associated with a greater incidence and severity of adverse effects than those of lower doses [22,23]. These adverse reactions typically dissipate once medication is discontinued.

Hepatitis is considered one of the less common adverse effects of isotretinoin. Emtenani et al. conducted a global population-based retrospective cohort study involving patients with acne who were prescribed isotretinoin ($n = 79{,}012$) [24]. The study found elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in 7.4% of cases, whereas elevated gamma-glutamyl transferase (GGT) levels were reported in 0.2% of cases. Among these, severely elevated ALT occurred in 0.1%, AST in 0.2%, and GGT in 0.02% of cases. These severe laboratory abnormalities were observed only within the first 1–3 months of initiating isotretinoin treatment. However, its impact was recognized as one of the most concerning side effects, as reported by 52.6% of patients and 54.7% of general physicians [25,26]. This concern often leads to frequent blood monitoring

of liver function tests, which can overwhelm patients [27]. Hobson et al. conducted a survey on isotretinoin monitoring trends related to liver function tests [28]. They found that over 60% of respondents check liver function tests at baseline, while 74% conduct monthly liver function test monitoring. Similarly, Barbieri et al. observed that although abnormal laboratory values were rare, the frequency of laboratory monitoring remained consistent throughout the 9.5-year study period [29]. We therefore primarily reviewed the incidence of isotretinoin-related hepatotoxicity to provide evidence-based justification for the appropriate frequency of liver function monitoring during isotretinoin therapy.

2. Methods

A narrative review of the literature on isotretinoin-induced hepatotoxicity in patients with acne was conducted, covering the search period from 1 January 2005 to 5 December 2024. The search was performed in PubMed (n = 24), Directory of Open Access Journals (DOAJ) (n = 11), and Scopus (n = 203) databases using the following keywords: "isotretinoin", "13-cis-retinoic acid", "hepatotoxicity", "liver toxicity", "liver injury", "hepatitis", "incidence", and "acne". Boolean operators (AND, OR) were used to refine the search strategy. After removing duplicates, 218 articles remained for screening. Publications were screened in two stages: title and abstract screening, which resulted in 78 articles selected for full-text review. Studies were included if they involved human participants aged 12–50 years, were published in English, and met the following criteria: observational studies, randomized controlled trials, cross-sectional studies, systematic reviews/meta-analyses, case reports, and case series. Exclusion criteria comprised animal studies, studies focusing on acne treatments not specific to isotretinoin, and studies lacking details on liver function tests. Two independent reviewers (WT and TK) performed the screening and selection processes and resolved any disagreements through discussion to reach a consensus. Ultimately, 44 articles meeting the inclusion and exclusion criteria were included in this narrative review to assess the incidence of isotretinoin-related hepatotoxicity and conclude optimal liver function monitoring during isotretinoin treatment.

3. Isotretinoin Usage in Acne Management

3.1. Pharmacokinetics of Isotretinoin

Details of the pharmacokinetics of isotretinoin, including the absorption, bioavailability, metabolism, distribution, and excretion of Accutane, Absorica, and Absorica LD, are shown in Table 1 [16,17].

Table 1. Pharmacokinetics of isotretinoin.

Pharmacokinetics	Accutane (Conventional Formulation)	Absorica (Lidose Formulation)	Absorica LD (Micronized Formulation)
Absorption and bioavailability	Oral absorption of Accutane is enhanced when taken with a high-fat meal. The mean $AUC_{0-\infty}$ and C_{max} of isotretinoin were 10,004 ng·h/mL and 862 ng/mL, respectively, under fed conditions, approximately 170% and 186% higher, respectively, compared with those of fasting conditions.	The mean AUC_{0-t} and C_{max} of isotretinoin were 6095 ng·h/mL and 369 ng/mL, respectively, under fed conditions, approximately 50% and 26% higher, respectively, compared with those of fasting conditions.	The mean AUC_{0-t} and C_{max} of isotretinoin were 10,209 ng·h/mL and 646 ng/mL, respectively, under fed conditions, approximately 20% and 6% higher, respectively, compared with those of fasting conditions.
Protein binding	99.9% bound to plasma proteins, primarily albumin.		

Table 1. *Cont.*

Pharmacokinetics	Accutane (Conventional Formulation)	Absorica (Lidose Formulation)	Absorica LD (Micronized Formulation)
Metabolism	Three metabolites are identified in human plasma: 4-oxo-isotretinoin, retinoic acid (tretinoin), and 4-oxo-retinoic acid (4-oxo-tretinoin). Retinoic acid and 13-cis-retinoic acid are geometric isomers that undergo reversible interconversion. Isotretinoin undergoes irreversible oxidation. The primary P450 isoforms involved in isotretinoin metabolism are CYP2C8, CYP2C9, CYP3A4, and CYP2B6. Isotretinoin and its metabolites are further metabolized into conjugates, which are excreted in urine and feces.		
Half-life elimination (h)	Isotretinoin: 21.0 ± 8.2 4-oxo-isotretinoin: 24.0 ± 5.3	Isotretinoin: 18 4-oxo-isotretinoin: 38	Isotretinoin: 24 4-oxo-isotretinoin: 38
T_{max} (h)	Fed: 5.3 Fasted: 3.2	Fed: 6.4 Fasted: 2.9	Fed: 5.0 Fasted: 3.5
Excretion	Its metabolites are excreted equally in feces and urine, totaling 65–83%.		

Note: AUC_{0-t}, Area Under the Curve from time zero to the last measurable concentration; $AUC_{0-\infty}$, Area Under the Curve from time zero to infinity; C_{max}, maximum concentration; T_{max}, time to peak. Data in Table 1 are derived from References [16,17].

3.2. Liver Function Test Patterns and the Mechanism of Isotretinoin and Hepatotoxicity

Drug-induced liver injury (DILI) can be categorized as direct (intrinsic), idiosyncratic, or indirect, based on distinct characteristics [30]. Direct DILI is dose-dependent, occurs within a short latency period (a few days), has a high rate of occurrence, and is predictable. It typically presents with acute liver damage, such as centrilobular necrosis or vascular injury, and is commonly caused by drugs, such as acetaminophen, nicotinic acid, and aspirin. This mechanism of action involves intrinsic hepatotoxicity. Idiosyncratic DILI is not dose-dependent, although a threshold dose may be required. It has a variable latency period (from days to months), occurs infrequently, and is often unpredictable. It manifests as acute hepatocellular injury, cholestatic damage, or chronic conditions and can be triggered by drugs, such as isoniazid, amoxicillin–clavulanate, macrolides, or fluoroquinolones. This mechanism involves metabolic dysfunction and immune-mediated damage. Indirect DILI is generally unrelated to the dose and is characterized by a delayed latency period (weeks to months). It occasionally occurs and involves drug-induced effects on immune responses or cholesterol regulation, leading to conditions, such as immune-mediated hepatitis and fatty liver disease. Examples include corticosteroids, immune checkpoint inhibitors, tumor necrosis factor inhibitors, and monoclonal antibodies.

Isotretinoin-induced liver injury is complex and may primarily manifest as idiosyncratic reactions, with a small number of cases exhibiting an autoimmune response [31–33]. The median time for liver function test abnormalities was 2 months (range: 1–3 months) [34]. Liver function elevations were observed in 19.6%, 33.3%, and 25.5% of the patients during the first, second, and third months of treatment, respectively. While the drug dose was once considered unimportant in idiosyncratic DILI, evidence suggests that high doses increase the likelihood of its occurrence. High doses can induce greater cellular stress, although individual variations in compensatory mechanisms influence the extent of the damage [30]. Blasiak et al. found that patients receiving isotretinoin at cumulative doses ≥220 mg/kg experienced elevated AST levels above 90 U/L in 6.4% of cases and ALT levels above 105 U/L in 1.3% of cases [35]. By contrast, no increase in these biomarkers was observed in patients treated with cumulative doses below 200 mg/kg. However, the association between daily and cumulative doses and the incidence and severity of hepatitis remains controversial. Öktem et al. reported abnormal liver function at isotretinoin doses of 40, 30, and 50 mg/d in 29.4%, 23.5%, and 19.6% of patients, respectively [34]. Additionally, changes in liver function, whether improved or deteriorated, were not significantly

correlated with dose adjustments ($p = 0.57$). Yaqoubi et al. demonstrated that chi-square analysis revealed no significant relation between dosage and liver function tests, including total bilirubin, total protein, ALT, albumin, globulin, and alkaline phosphatase (ALP) [36]. Similarly, Alajaji et al. found no statistically significant association between total cumulative dose and abnormalities in ALT or AST levels [37]. Abd-Elaziz et al. also observed a weak positive correlation between the dose and duration of isotretinoin use and elevated AST and ALT levels [38]. Additionally, Özaslan et al. demonstrated that there was no correlation between the cumulative dose and AST, ALT, or GGT levels [39]. Further studies are needed to determine whether a threshold dose or cutoff exists that would warrant increased awareness and monitoring of laboratory parameters.

It is thought to involve multiple mechanisms, including oxidative stress caused by reactive oxygen species (ROS) and insufficient antioxidant defense. Drug metabolism primarily occurs in the liver and involves extensive aerobic metabolic activity. This metabolic process inevitably results in the production of ROS. The cytochrome P450 enzyme system, which is crucial for drug metabolism, produces reactive intermediates that contribute to ROS generation [40]. The liver has multiple antioxidant mechanisms that combat the detrimental effects of ROS. These defense systems include both enzymatic and nonenzymatic antioxidants. Enzymatic antioxidants include superoxide dismutase, catalase, and glutathione (GSH) peroxidase, whereas nonenzymatic antioxidants include vitamins C and E [41]. When antioxidant defenses are overwhelmed by excessive ROS generation during drug metabolism, cellular signaling cascades can be triggered. These cascades result in impaired mitochondrial function, increased autophagy, and cell death via apoptosis and necrosis. Oxidative stress damages the cells, promotes inflammation, and contributes to various hepatic disorders [42].

Given the limited human data on isotretinoin-induced hepatotoxicity mechanisms, animal studies offer valuable insights into underlying processes. Daye et al. investigated the effects of isotretinoin on oxidative damage in 30 Wistar albino rats divided into four groups: a control group and three isotretinoin treatment groups (treated for 1, 2, and 3 months) [43]. Isotretinoin was orally administered at a daily dose of 7.5 mg/kg. At the end of each treatment period, the blood, liver, and muscle tissues were collected and analyzed for various oxidative stress markers. Significant differences in ALT levels were observed between the control group and the third-month isotretinoin treatment group. Furthermore, the levels of oxidative stress markers in the liver, including malondialdehyde, protein carbonyl, and glutathione (GSH), were significantly higher in rats treated with isotretinoin for 3 months than in those treated for 1 month. This change was attributed to the cumulative isotretinoin dose. Oxidative stress occurs when excess ROS disrupt the oxidant–antioxidant balance, leading to inflammation, tissue damage, and cellular biomolecular damage. Highly reactive ROS, such as superoxide anions and hydroxyl radicals, are particularly damaging because they contain unpaired electrons [44]. Georgala et al. enrolled 18 patients with cystic acne to receive isotretinoin (0.5 mg/kg/d) for 45 d and compared them to 22 controls [45]. The total antioxidant status in the treatment group (1335 ± 93) was significantly lower than that in the control group (1536 ± 126), $p = 0.040$. Additionally, 8-hydroxy-2-deoxyguanosine, an indicator of deoxyribonucleic acid damage, was significantly higher in the treatment group (0.21 ± 0.03) compared with that in controls (0.07 ± 0.01), $p < 0.001$. Erturan et al. studied 31 patients with nodulocystic acne who received oral isotretinoin at a dose of 0.5 to 0.7 mg/kg/d for 2 months [46]. The study found that plasma vitamin E levels were significantly lower in the treatment group than in the pretreatment group, whereas GSH and GSH peroxidase levels significantly increased. Ozkol et al. measured paraoxonase-1 activity in patients with acne vulgaris who took isotretinoin at a daily dose of 0.5 to 0.75 mg/kg of body weight for at least 5 months [47].

After treatment, they observed a significant decrease in paraoxonase-1 activity, an increase in the total oxidant status and oxidative stress index values, and a slight reduction in total antioxidant capacity.

The interplay between genetic factors and the effects of isotretinoin on liver enzymes highlights individual susceptibility to treatment-related complications. One notable study by Alzoubi et al. focused on the effect of isotretinoin on biochemical parameters, including liver enzymes, such as AST and ALT [48]. Analysis of the rs2715554 polymorphism in RARA revealed that individuals with the TC genotype experienced a greater increase in AST levels following isotretinoin treatment than those with the TT genotype. This suggests that genetic variations may play a role in susceptibility to elevated liver enzyme levels, potentially increasing the risk of liver-related complications during isotretinoin therapy [48].

3.3. Incidence of Hepatitis and Elevated Liver Enzymes

Isotretinoin is also associated with hepatitis and a range of adverse gastrointestinal events. Vallerand et al. reported that 15 of 751 (2.0%) patients treated with isotretinoin experienced gastrointestinal side effects [49]. Among the controls, five of 388 (1.3%) patients withdrew because of nausea, vomiting, diarrhea, or abdominal pain, all of which occurred in the antibiotic groups. Additionally, one isotretinoin-treated patient (1/372, 0.3%) withdrew owing to decreased appetite.

Based on our search results, we identified six large-sample studies with sample sizes of greater than 1000. Mild elevations in liver enzymes are more common, occurring in up to 11%, while the range of reported incidences for isotretinoin-induced hepatitis (grade $\geq$ 3 abnormalities) is approximately 0.2% to 0.5%. The relevant studies are presented in Table A1. Zane et al. conducted a retrospective cohort study involving 13,772 participants between 1995 and 2002 [50]. The median duration of the treatment course was 21 weeks, with a median cumulative dose of 9 g and a median calculated daily dose of 65 mg. Liver function tests, assessed using AST or ALT levels, revealed the following distribution: grade 1 (41–100) in 1004 participants (9.8%), grade 2 (101–200) in 89 participants (0.9%), grade 3 (201–800) in 13 participants (0.1%), and grade 4 (>800) in one participant (0.01%). Rademaker et al. performed a retrospective chart review over a 6-year period involving 1743 patients to examine adverse drug reactions associated with isotretinoin [51]. Most patients received a dose of 1 mg/kg/d, with a cumulative dose ranging from 150 to 160 mg/kg. Significantly abnormal liver function test results were observed in 20 patients (1.1%). Lee et al. performed a meta-analysis of 26 studies including 1574 patients [52]. The analysis found that many studies have reported no significant elevation in liver function during isotretinoin therapy. The mean AST value during treatment was 22.67 U/L (99% CI, 19.94–25.41 U/L), with a mean increase of 3.72 U/L (99% CI, 2.44–5.01 U/L) from baseline to follow-up at 6.6 weeks. Mid-treatment analyses showed differences of 4.52 U/L (99% CI, 2.91–6.13 U/L) at 6 weeks and 3.72 U/L (99% CI, 2.34–5.09 U/L) at 8 weeks. The mean ALT value during treatment was 21.77 U/L (99% CI, 18.96–24.59 U/L), with a mean increase of 3.22 U/L (99% CI, 0.99–5.45 U/L) from baseline to follow-up at 6.5 weeks. Brzezinski et al. conducted a retrospective review of 3525 patients treated for acne vulgaris over a 5-year observation period [53]. The isotretinoin dose was adjusted based on body weight, with an average weight of 65.74 kg (SD, 16.73). The minimum cumulative dose was 13,546 mg, whereas the maximum cumulative dose was 118,400 mg. The mean treatment duration was 9.3 months (SD, 1.10), ranging from 7 to 13 months. An increase in liver enzyme levels was observed after treatment, with 68 participants (2.09%) showing above-normal levels. Additionally, one patient experienced an increase in bilirubin levels. Barbieri et al. conducted a retrospective study involving 1863 patients with a median age

of 18.2 years (IQR, 16.3–24.5) [29]. The median duration of isotretinoin treatment was 148 d (IQR, 65–183 d); however, cumulative dose data were unavailable. Grade 3 AST and ALT abnormalities (5× ULN–20× ULN) were noted in <0.5% of patients, with no cases of grade 4 abnormalities (>20× ULN). Among the five patients who developed Grade 3 AST or ALT abnormalities, four (80%) showed improvement upon recheck, and three (60%) continued their isotretinoin course. Recently, Emtenani et al. conducted a global population-based retrospective cohort study of 158,024 participants [24]. Compared to systemic antibiotics, isotretinoin treatment in acne patients increased the risk of elevated liver enzymes: alanine aminotransferase (ALT, hazard ratio [HR] 4.00), aspartate aminotransferase (AST, HR 4.90), and gamma-glutamyl transferase (GGT, HR 1.41). It also raised the risk of grade $\geq$ 3 AST elevation within three months (HR 1.45), with no significant association for grade $\geq$ 3 ALT or GGT abnormalities.

The Common Terminology Criteria for Adverse Events (version 5.0) is commonly used to define and evaluate the severity of adverse events based on elevated liver function tests and are categorized into grades one to four [54]. The selected elements of the liver function test results, including AST, ALT, ALP, bilirubin, and GGT, are shown in Table 2.

Table 2. Selected elements of liver function test results based on Common Terminology Criteria for Adverse Events (CTCAE).

CTCAE Term	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-Threatening)
ALT (U/L)	>ULN–3.0× ULN; 1.5–3.0× baseline	>3.0–5.0× ULN; >3.0–5.0× baseline	>5.0–20.0× ULN; >5.0–20.0× baseline	>20.0× ULN; >20.0× baseline
AST (U/L)	>ULN–3.0× ULN; 1.5–3.0× baseline	>3.0–5.0× ULN; >3.0–5.0× baseline	>5.0–20.0× ULN; >5.0–20.0× baseline	>20.0× ULN; >20.0× baseline
ALP (U/L)	>ULN–2.5× ULN; 2.0–2.5× baseline	>2.5–5.0× ULN; >2.5–5.0× baseline	>5.0–20.0× ULN; >5.0–20.0× baseline	>20.0× ULN; >20.0× baseline
Total Bilirubin (mg/dL)	>ULN–1.5× ULN; 1.0–1.5× baseline	>1.5–3.0× ULN; >1.5–3.0× baseline	>3.0–10.0× ULN; >3.0–10.0× baseline	>10.0× ULN; >10.0× baseline
GGT (U/L)	>ULN–2.5× ULN; 2.0–2.5× baseline	>2.5–5.0× ULN; >2.5–5.0× baseline	>5.0–20.0× ULN; >5.0–20.0× baseline	>20.0× ULN; >20.0× baseline

Note: CTCAE, Common Terminology Criteria for Adverse Events; ULN, upper limit of normal; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl Transferase; ALP, alkaline phosphatase.

3.4. How to Monitor and Prevent Liver Function Abnormalities?

Most studies recommend baseline liver function testing followed by early monitoring (within 1–3 months) and further testing only if clinical abnormalities are noted [24,50,52,53]. Laboratory changes during isotretinoin treatment were statistically significant, though most lacked clinical relevance. Increases in transaminase levels were mild and resolved spontaneously [50]. Monthly laboratory testing is common for patients on standard doses with average risk profiles; however, most mild elevations are not clinically significant and do not inform dose adjustment decisions [29,52]. Frequent testing beyond this is not generally supported unless clinically indicated [29].

The hepatitis pattern of isotretinoin-induced liver injury typically presents as hepatocellular damage, often marked by elevated levels of liver enzymes, such as ALT and AST. It may also present as a mixed pattern, combining features of hepatitis and cholestasis, characterized by elevated ALP and GGT levels, similar to other retinoids, such as acitretin [52,55]. A Delphi consensus study on laboratory monitoring of isotretinoin was conducted by an international group of 22 clinical and research experts specializing in acne [56]. This study recommends checking ALT within a month before starting treatment

and again at the peak dose. However, routine testing of GGT, bilirubin, albumin, and total protein levels is not recommended. No consensus has been reached regarding the necessity of testing AST or ALP levels. ALT is considered a more liver-specific marker than AST, as ALT is primarily found in the liver, whereas AST is also present in cardiac and skeletal muscles, as well as erythrocytes. This distinction makes ALT a more accurate indicator of liver damage and helps minimize unnecessary follow-up testing that might arise from nonspecific elevations in AST [57,58]. Monitoring ALT levels is cost-effective and logistically feasible, particularly in resource-limited settings [59]. However, Emtenani et al. recently conducted a large population-based retrospective cohort study, revealing that compared with that of patients with acne treated with oral antibiotics, those receiving isotretinoin had a higher risk of grade ≥ 3 elevated AST levels (HR, 1.45; 95% CI, 1.13–1.85; $p = 0.003$) within the first 3 months of treatment [24]. By contrast, no significant risk was observed for grade ≥ 3 impairment in ALT or GGT levels among isotretinoin users. These findings highlight the potential gap between expert recommendations and recent observational data, suggesting the need for a more tailored approach for laboratory monitoring during isotretinoin treatment [56]. While ALT is widely accepted as the preferred marker for liver function owing to its specificity, Emtenani et al. indicated that AST elevations may require closer observation, particularly during the initial months of treatment [24]. This raises critical questions regarding whether current monitoring practices sufficiently address all liver-related risks associated with isotretinoin. Consistent with the findings of Tosun et al., isotretinoin administered at 0.5–1 mg/kg for 3 months resulted in a significant increase in AST levels from 17.349 ± 0.433 to 19.241 ± 0.302 by the third month ($p < 0.001$), whereas ALT levels showed no significant change ($p = 0.455$) [60]. Soutou et al. found the strongest correlation between abnormal AST levels and the use of isotretinoin, particularly the brand Acnotren ($p = 0.009$) [61]. Özaslan et al. reported that ALT levels showed no significant changes among baseline, the 2nd month, and the 4th month [39]. In contrast, AST levels significantly increased from a baseline mean of 16.81 ± 5.41 to 22.10 ± 19.22 at the 2nd month ($p < 0.001$) and 21.09 ± 9.87 at the 4th month ($p < 0.001$), with no significant difference between the 2nd and 4th months ($p = 0.637$). Further research is needed to better understand the clinical significance of AST elevation and evaluate whether routine monitoring of both ALT and AST levels could enhance the safety and effectiveness of isotretinoin therapy, taking cost considerations into account.

Regarding recovery from DILI, Pona et al. conducted a study involving 108 participants, with 79 receiving 80 mg of isotretinoin and 23 receiving 40 mg of isotretinoin daily [62]. Most liver enzyme abnormalities occurred during the first month of therapy (48 cases). Grade 1 abnormalities often resolve with minimal intervention, whereas severe cases require treatment adjustments. For Grade 1 abnormalities, most patients continued isotretinoin (69% for AST and 65% for ALT), with normalization rates of 31% (AST) and 27% (ALT) within 6–7 weeks. Persistent ALT elevations were observed in 33% of the patients, while follow-up was unavailable for 8% (AST) and 6% (ALT). For Grade 2 abnormalities, some patients required dose adjustments or discontinuation, with normalization occurring within 1–4 weeks. For Grade 3, most patients discontinued isotretinoin, and AST levels normalized within 2 weeks. Consistent with the findings of Öktem et al., changes in liver function were not associated with dose adjustments, regardless of whether they were increased or decreased ($p = 0.57$) [34]. Therefore, routine testing for AST and ALT levels may not be necessary in patients with minor liver enzyme abnormalities receiving isotretinoin.

In clinical practice, potential drug–drug interactions are another important issue that should be carefully considered [63–67]. Common inducers, which can lower the plasma levels of isotretinoin and potentially reduce its therapeutic efficacy, and common inhibitors,

which can increase isotretinoin levels and the risk of toxicity and adverse effects, are summarized in Table 3.

Table 3. Common inducers and inhibitors of isotretinoin metabolism and their potential effects on plasma levels and therapeutic outcomes.

Cytochrome Isoform	Inducers	Inhibitors
CYP2C8	Phenytoin, Progesterone, Rifampin, and Ritonavir	Gemfibrozil, Trimethoprim, Efavirenz, and Clopidogrel
CYP2C9	Rifampin, Phenobarbital, and Dexamethasone	Tienilic acid, Suprofen, and Silybin
CYP3A4	Rifampin, Carbamazepine, Phenytoin, and Ritonavir	Clarithromycin, Erythromycin, Ritonavir, Delavirdine, Fluoxetine, Fluvoxamine, Verapamil, Diltiazem, and Ketoconazole
CYP2B6	Phenobarbital, Phenytoin, and Rifampin	Clopidogrel, Ticlopidine, and Efavirenz

Note: CYP, cytochrome.

In animal models, several antioxidant agents, including selenium, taurine, curcumin-rich turmeric extract, cumin oil, and isoflavones, have demonstrated potential in protecting against isotretinoin-induced liver injury by mitigating oxidative stress and enhancing antioxidant defenses [44,68–71]. However, Kus et al. conducted a study in which 82 patients were randomly assigned to one of two treatment groups: isotretinoin (1 mg/kg/d) alone or in combination with vitamin E (800 IU/d) for 16 weeks [72]. The results indicated that 800 IU/d of vitamin E did not reduce the side effects of isotretinoin (1 mg/kg/d) in acne vulgaris treatment. The rate of abnormal AST levels was 2.6% in the isotretinoin group and 11.1% in the combination group ($p = 0.188$), whereas the rate of abnormal ALT levels was 5.1% in the isotretinoin group and 8.3% in the combination group ($p = 0.666$). Further clinical studies are needed to validate these findings and optimize the use of antioxidant agents in clinical settings.

Moreover, several dietary supplements commonly used by individuals with acne have been linked to hepatotoxicity, which can lead to hepatitis. These include protein supplements, anabolic–androgenic steroids, creatine, herbal supplements, and pyridoxine (vitamin B6) and cyanocobalamin (vitamin B12) [73–77]. It is crucial for dermatologists to inquire about the use of these supplements in patients with acne and educate them about the potential risks associated with their consumption. Although uncommon, elevated AST levels in patients receiving isotretinoin could be attributed to prolonged plasma exposure to disintegrating platelets in a transported plasma separator tube, improper tube selection, or iatrogenic hemolysis caused by the use of an overly small venipuncture needle. If such causes are suspected, the error should be corrected, and the test should be repeated to confirm the results [78].

4. Further Considerations

Despite the widespread use of isotretinoin, there is a notable lack of robust, large-scale, long-term prospective studies evaluating its effects on liver function over time. Addressing this gap in data could greatly enhance our understanding of the chronic implications of isotretinoin-induced liver enzyme elevation, including the trends of transient and persistent elevations. Variability in study design, differences in cumulative isotretinoin doses, timing of liver function testing, and definitions of abnormal enzyme levels complicate data synthesis. These inconsistencies make it challenging to draw definitive conclusions

and highlight the need for standardized protocols in future research to enable meaningful meta-analyses.

The current guideline, based on Delphi consensus, recommends checking ALT levels within a month before starting treatment and again at the peak dose [56]. To apply this guideline effectively in clinical practice, several considerations need to be addressed. First, it is important to consider whether routine ALT monitoring is necessary for all patients. Large-scale studies report a low incidence (around 1–2%) of elevated liver function tests during isotretinoin treatment [51,53]. Most studies have shown no significant elevations in liver function tests during therapy [29,52]. There is limited research focusing on patients who may be at higher risk for abnormal liver function tests. These studies could help identify which patients require closer monitoring while taking isotretinoin. Second, the use of ALT as the sole recommended parameter for safety monitoring may warrant reconsideration. A recent large-scale study found that patients with acne treated with isotretinoin had a significantly higher risk—around 1.5 times—of developing grade ≥ 3 elevated AST levels within the first three months compared to those receiving oral antibiotics [24]. This finding suggests that AST may be a more sensitive indicator for monitoring liver function, and incorporating AST measurements alongside ALT in safety monitoring protocols could enhance the early detection of significant liver enzyme elevations in at-risk patients. Third, the guideline does not specify the optimal frequency for checking ALT levels during treatment. Additionally, the relationship between daily dose, cumulative dose, and the incidence or severity of hepatitis remains a topic of debate. Prior to guideline implementation, additional research is necessary to identify whether a defined threshold dose or cutoff level warrants heightened monitoring and closer observation of laboratory parameters. Fourth, the protocol for dose adjustments in response to abnormal liver function test results is currently poorly defined. This uncertainty creates challenges for clinicians to balance the risks of liver injury with the therapeutic benefits of isotretinoin. Observational studies tracking patients with abnormal liver function during isotretinoin treatment to identify patterns, thresholds, and outcomes, or randomized controlled trials comparing different dose-adjustment strategies, could help establish a more comprehensive and effective protocol. Fifth, various isotretinoin regimens are currently used to treat acne, including conventional, low-dose, intermittent, and stepwise dose reduction regimens. These different approaches may influence the patterns of abnormal liver function tests, suggesting that monitoring strategies should be tailored to each specific regimen. It is anticipated that a comprehensive guideline will provide optimal recommendations for monitoring, ensuring timely detection and prevention of severe liver injury while minimizing unnecessary resource utilization and supporting practical implementation in diverse healthcare settings.

5. Review Limitations

This study presents a narrative review, which is inherently limited by its design. However, we employed a structured search strategy and applied clear inclusion and exclusion criteria across three database resources, as outlined previously. Expert opinions, editorials, and non-systematic reviews were not in the inclusion criteria to maintain a focus on robust, evidence-based data from original research or comprehensive reviews. While these sources may be valuable for context or background information, they do not typically provide the same level of empirical and high-quality evidence required to support the conclusions of this narrative review. By incorporating a broad range of sources, we aimed to provide a more comprehensive overview of the topic, identify gaps in the literature, and highlight areas for future research. Most studies, even those with large sample sizes, reported ranges for isotretinoin cumulative dosages and abnormal liver function test levels

without specifying precise values or the exact timing relative to isotretinoin initiation. The assessment of isotretinoin's safety concerning hepatitis relies heavily on retrospective reports, which may contain incomplete data. Additionally, other factors influencing liver function tests may have affected these findings. These limitations make it challenging to summarize the data and draw valid conclusions. Furthermore, our review was limited to full-text articles published in English. This restriction may have led to the exclusion of relevant studies published in other languages, potentially introducing language bias into our findings.

6. Conclusions

Isotretinoin remains a critical component in the management of moderate to severe acne, providing significant clinical benefits. However, its potential for hepatotoxicity, albeit rare, necessitates vigilant monitoring. The findings of this review suggest that mild elevations in liver enzymes occur more frequently and are generally transient, while severe hepatotoxicity is uncommon. Current evidence supports the practice of routine initial and early follow-up monitoring of liver function, with emphasis on ALT as a specific indicator of hepatic injury. The potential significance of AST in safety protocols, particularly during the initial months of treatment, warrants further investigation. To optimize patient safety, it is imperative to adopt an individualized approach to laboratory monitoring based on patient-specific risk factors and treatment regimens. The integration of genetic and oxidative stress markers into monitoring protocols may enhance the identification of susceptible individuals and refine treatment strategies. Comprehensive, prospective studies are necessary to address gaps in long-term hepatotoxicity data and to establish standardized monitoring protocols. These advancements will facilitate the optimization of the risk–benefit profile of isotretinoin therapy, potentially leading to improved outcomes for patients with acne.

Author Contributions: Conceptualization, W.T.; methodology, W.T.; validation, W.T.; formal analysis, W.T.; investigation, W.T.; resources, W.T.; data curation, W.T.; writing—original draft preparation, W.T.; writing—review and editing, W.T. and C.E.; supervision, T.K.; project administration, T.K. All authors have read and agreed to the published version of the manuscript.

Funding: This work was partially supported by Walailak University under the international research collaboration scheme (WU-CIA-04407/2024).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: All data supporting the reported results are included in this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Table A1. Studies on the relation between isotretinoin and hepatotoxicity.

Authors, Year	Country	Study Design (*n*)	Isotretinoin Dosage	Main Findings According to the Abnormal Liver Function Test
Alrasheed et al., 2024 [79]	Saudi Arabia	Retrospective study (515)	10–60 mg/day for at least 3 months	Baseline and during-treatment comparisons showed a significant increase in AST with a mean difference of 4.24 ($p < 0.001$) and in ALT with a mean difference of 2.93 ($p < 0.001$).
Emtenani et al., 2024 [24]	NA	Retrospective study (158,024)	NA	Patients with acne treated with isotretinoin demonstrated a higher risk of developing elevated liver enzyme levels: ALT (HR 4.00, 95% CI 3.77–4.23, $p < 0.001$), AST (HR 4.90, 95% CI 4.61–5.22, $p < 0.001$), and GGT (HR 1.41, 95% CI 1.09–1.82, $p = 0.008$). Additionally, isotretinoin use was associated with an increased risk of grade ≥ 3 AST elevation within the first three months (HR 1.45, 95% CI 1.13–1.85, $p = 0.003$) compared to systemic antibiotics. However, no significant association was observed between isotretinoin treatment and grade ≥ 3 abnormalities in ALT or GGT levels.
Li et al., 2024 [80]	China	Retrospective study (388)	0.2–0.4 mg/kg/d with a cumulative dose of 120 mg/kg	Thirty-two patients (8.2%) and twenty-eight patients (7.2%) exhibited elevated serum levels of ALT and AST, respectively. The time from treatment initiation to the detection of abnormalities was 67 ± 35 d for ALT and 73 ± 22 d for AST. The mean levels observed were 88 ± 33.6 U/L for ALT and 52.6 ± 24.1 U/L for AST.
Maden, 2024 [81]	Cyprus	Retrospective study (136)	0.3–0.5 mg/kg/day for at least 3 months	At baseline, mean ALT, AST, and GGT levels were 18.86 ± 9.64 U/L, 17.96 ± 4.77 U/L, and 16.96 ± 8.26 U/L, respectively. By the third month, these levels increased to 22.36 ± 13.96 U/L, 21.03 ± 6.75 U/L, and 19.30 ± 9.24 U/L, with all changes being statistically significant ($p \leq 0.001$).
Yaqoubi et al., 2024 [36]	Oman	Retrospective study (50)	46% received 20 mg/d, 54% received 30 mg/d, and 57% were treated for 1 month.	The mean ALT increased significantly from 13.78 ± 6.87 to 18.88 ± 10.79 U/L ($p < 0.05$), and the mean total bilirubin rose from 7.50 ± 3.15 to 9.70 ± 5.35 µmol/L ($p < 0.05$). No significant differences were observed in total protein, albumin, globulin, or alkaline phosphatase levels before and after treatment. Chi-square analysis showed no significant relation between dosage and liver function tests, including total bilirubin, total protein, ALT, albumin, globulin, and alkaline phosphatase.

Table A1. *Cont.*

Authors, Year	Country	Study Design (*n*)	Isotretinoin Dosage	Main Findings According to the Abnormal Liver Function Test
Al Dhafiri et al., 2023 [82]	Saudi Arabia	Retrospective study (97)	10–40 mg/d over 6 months	At baseline, elevated AST levels were observed in three patients (3.1%), whereas elevated ALT levels were noted in two patients (2.1%). By the final readings, the number of patients with elevated AST increased to eight (8.2%), and those with elevated ALT rose to four (4.1%).
Özaslan et al., 2023 [39]	Turkey	Retrospective study (415)	The mean cumulative dose was 7267.27 ± 1878.4 mg	ALT levels showed no significant changes among baseline, the 2nd month, and the 4th month. In contrast, AST levels significantly increased from a baseline mean of 16.81 ± 5.41 to 22.10 ± 19.22 at the 2nd month ($p < 0.001$) and 21.09 ± 9.87 at the 4th month ($p < 0.001$), although there was no significant difference between the 2nd and 4th months ($p = 0.637$). Similarly, GGT levels significantly increased from a baseline mean of 15.89 ± 8.00 to 19.59 ± 11.83 at the 2nd month ($p < 0.001$) and 18.77 ± 11.74 at the 4th month ($p < 0.001$), with no significant difference between the 2nd and 4th months ($p = 0.212$).
Soutou et al., 2023 [61]	Lebanon	Retrospective study (468)	The median cumulative dose was 8400 mg (range: 7100–10,000 mg)	AST levels exceeding 1.5 times the upper limit of normal were observed in 1.9% of patients, whereas ALT levels exceeding 1.5 times the upper limit were seen in 2.8%. Abnormal AST levels were significantly associated with the use of Acnotren ($p = 0.009$).
Parthasarathy et al., 2022 [83]	USA	Retrospective study (130)	NA	Liver enzyme levels showed no significant changes. AST abnormalities decreased from 18.5% to 14.6% (Grade 1) and from 1.5% to 0.8% (Grade 2), with no Grade 3 cases. ALT remained at 20.0% (Grade 1) and decreased from 1.5% to 0.8% (Grade 2), with no Grade 3 cases.
Tosun et al., 2022 [60]	Turkey	Retrospective study (143)	0.5–1 mg/kg for 3 months	AST levels significantly increased from 17.349 ± 0.433 to 19.241 ± 0.302 at the third month ($p < 0.001$), whereas ALT levels showed no significant difference ($p = 0.455$).
Alajaji et al., 2021 [37]	Saudi Arabia	Retrospective study (407)	The mean cumulative dose was 6741.94 ± 253.7 mg	At baseline, AST was elevated in 5.4% of patients and ALT in 12.7%. By the last visit, elevations decreased to 3.9% for AST and 9% for ALT. No statistically significant relation was found between the total cumulative dose and ALT or AST abnormalities.
Al-Haddab et al., 2021 [84]	Saudi Arabia	Retrospective study (386)	A median dose of 30 mg/d for at least 4 weeks	The percentage of abnormal AST or ALT did not change significantly among baseline, the first follow-up, and the second follow-up.

Table A1. *Cont.*

Authors, Year	Country	Study Design (*n*)	Isotretinoin Dosage	Main Findings According to the Abnormal Liver Function Test
Pona et al., 2021 [62]	USA	Retrospective study (108)	Approximately 79 participants received 80 mg/d and 23 received 40 mg/d of isotretinoin.	Overall, Grade 1 abnormalities often resolved with minimal intervention, whereas severe grades required treatment changes. For Grade 1 abnormalities, most patients maintained isotretinoin (69% for AST, 65% for ALT), with normalization in 31% (AST) and 27% (ALT) within 6–7 weeks. Persistent ALT elevations occurred in 33%, and 8% (AST) and 6% (ALT) lacked follow-up. For Grade 2, a few patients required dose adjustments or discontinuation, with normalization in 1–4 weeks. For Grade 3, most patients discontinued isotretinoin, and AST normalized within 2 weeks.
Shah et al., 2021 [85]	USA	Retrospective study (903)	20–160 mg/day for 4–9 months to achieve cumulative dose of 120–150 mg/kg	ALT levels increased from 20.6 ± 7.3 at baseline to 24.3 ± 10.4 at the 3rd month, then decreased to 21.6 ± 15.1 at the 6th month, with abnormalities detected at 23.0 ± 3.4 weeks (84.9% at 1–3 months, 15.0% at 4–6 months). AST levels increased from 20.9 ± 14.4 at baseline to 22.8 ± 15.2 at the 3rd month and decreased to 21.2 ± 17.1 at the 6th month, with abnormalities detected at 13.9 ± 5.1 weeks (79.4% at 1–3 months, 20.5% at 4–6 months). Isotretinoin doses were reduced due to ALT in 13.3% and AST in 8.8%, with discontinuation in 0.9% for ALT and none for AST.
Varol FI et al., 2021 [32]	Turkey	Case report (1)	60 mg/d	At week 3, AST rose from 36 to 102 U/L and ALT from 43 to 130 U/L, prompting a dose reduction to 40 mg/d, then discontinuation as levels reached 145 U/L (AST) and 214 U/L (ALT). Liver biopsy confirmed autoimmune hepatitis. Prednisolone and azathioprine were initiated, normalizing transaminase levels within a month.
Akouch et al., 2021 [86]	Lebanon	Case report (1)	40 mg/d for 8 months	The patient developed severe abnormal liver function tests, with a diagnosis of acute liver failure caused by idiosyncratic drug-induced liver injury. The planned liver transplant was canceled because of the patient's clinical instability.
Abd-Elaziz et al., 2020 [38]	Egypt	Cross-sectional study (285)	37.2% took 40 mg/d, 36.8% took 80 mg/d, 17.5% took 60 mg/d, and 8.4% took 20 mg/d. Treatment durations were 4–6 months (36.5%), 3 months (30.2%), 2 months (20.4%), and 1 month (12.9%).	Nearly 30% of cases showed elevated ALT levels, whereas 23.2% had elevated AST levels. ALT significantly increased from 24.95 ± 5.18 before treatment to 40.06 ± 12.95 after treatment ($p < 0.001$). Similarly, AST rose from 24.46 ± 4.84 to 37.48 ± 11.21 ($p < 0.001$).

Table A1. *Cont.*

Authors, Year	Country	Study Design (*n*)	Isotretinoin Dosage	Main Findings According to the Abnormal Liver Function Test
Acar et al., 2020 [87]	Turkey	Case report (1)	45-day duration (dose unspecified)	The patient presented with AST levels of 848 U/L, ALT levels of 593 U/L, total bilirubin of 21 mg/dL, direct bilirubin of 16 mg/dL, and albumin of 4.1 g/dL. A liver biopsy revealed centrilobular, bridging, and panlobular necrosis, consistent with active acute hepatitis. The patient ultimately underwent a living donor liver transplantation.
Barbieri et al., 2020 [29]	USA	Retrospective study (1863)	The median course duration was 148 d (range: 65–183 d).	Grade 3 AST and ALT abnormalities were observed in fewer than 0.5% of screened patients and were not more frequent during therapy compared to baseline. Among the five patients who developed Grade 3 AST or ALT abnormalities, four (80%) showed improvement upon rechecking, and three (60%) were able to continue their isotretinoin treatment. No Grade 4 abnormalities were reported.
Tkachenko et al., 2020 [88]	USA	Retrospective study (735)	The mean cumulative dose was 126.9 ± 55.8 mg/kg.	A total of 139 patients (18.9%) had baseline laboratory abnormalities, with ALT elevations observed in 5.3% (n = 18). During treatment, 18 patients (5.3%) experienced ALT abnormalities. Among these, 10 required treatment modifications, including five with interrupted treatment and four who terminated treatment due to ALT elevation.
Aktas et al., 2019 [89]	Turkey	Retrospective study (50)	The mean daily isotretinoin dose for 6 months was 10 mg for 24 patients, 20 mg for 20 patients, and 30 mg for 6 patients.	Isotretinoin did not affect serum ALT or AST levels, except in one patient with an ALT of 59 U/L. All others had normal liver enzyme levels. The mean ALT and AST levels were 16 U/L and 22 U/L, respectively.
Nazarian et al., 2019 [90]	USA	Case report (1)	30–40 mg twice daily after 2 months for refractory acne.	By the third month, acne improved, but ALT rose to 175 U/L, leading to discontinuation. ALT peaked at 288 U/L 4 weeks later, and cholestyramine (4 g daily) was initiated. ALT normalized within a month and returned to baseline in 2 months. Isotretinoin was restarted 3 years later for cystic acne, with normal liver function throughout 5 months of treatment.

Table A1. *Cont.*

Authors, Year	Country	Study Design (*n*)	Isotretinoin Dosage	Main Findings According to the Abnormal Liver Function Test
Öktem et al., 2019 [34]	Turkey	Retrospective study (704)	30–50 mg/d	The doses of isotretinoin associated with abnormal liver function were 40 mg/d, 30 mg/d, and 50 mg/d, occurring in 29.4%, 23.5%, and 19.6% of patients, respectively. The maximum ALT and AST values observed during laboratory monitoring were 87 U/L and 97 U/L, respectively. Liver function elevations were noted in the first, second, and third months of treatment in 19.6%, 33.3%, and 25.5% of patients, respectively, with the median time of abnormalities occurring in the second month (range: 1–3 months). Alterations in liver function (recovery or worsening) were not significantly associated with dose adjustments ($p = 0.57$).
Vallerand et al., 2018 [49]	NA	Systematic review (751)	0.5–5.0 mg/kg/d for 12–32 weeks	Overall, abnormal bloodwork occurred in 15 out of 751 patients (2.0%) treated with isotretinoin, primarily involving elevated serum lipids or liver enzymes, compared to five out of 751 (0.7%) in the control group. Two patients (0.5%) randomized to isotretinoin withdrew from trials because of elevated liver enzymes.
Brzezinski et al., 2017 [53]	Poland and Romania	Retrospective study (3525)	The minimal cumulative dose was 118,400 mg and maximum was 13,546 mg. The mean treatment duration was 9.3 ± 1.10 months, ranging from 7 to 13 months.	There was an increase in liver enzyme levels following treatment, with 68 participants (2.09%) showing values above the normal range. Additionally, one patient experienced an elevation in bilirubin levels.
Webster et al., 2017 [91]	USA	Retrospective study (246)	The peak isotretinoin dosage is around 1 mg/kg.	A total of 35 (14.2%) patients had elevated AST levels, and 32 (13.0%) had elevated ALT levels. Elevated GGT levels were observed in 13 participants (5.3%), with eight participants (3.3%) experiencing GGT elevation accompanied by elevated AST or ALT levels.
Yap et al., 2017 [92]	Malaysia	Prospective study (150)	The mean cumulative dose was 98.8 ± 6.05 mg/kg.	Mild, transient elevations in liver enzymes, less than twice the upper limit of normal, were detected in five patients (3.3%).
Bugdayci et al., 2016 [93]	Turkey	Retrospective study (102)	The mean dose was 20 mg/d over a 24-week period.	AST levels (U/L) increased from 17.20 ± 5.15 at baseline to 18.28 ± 4.23 at 1 month and 19.24 ± 5.38 at 6 months of follow-up. ALT levels (U/L) showed a slight increase from 15.79 ± 7.87 at baseline to 15.84 ± 7.48 at 1 month and 16.75 ± 10.18 at 6 months. These changes were statistically significant ($p < 0.05$).

Table A1. *Cont.*

Authors, Year	Country	Study Design (*n*)	Isotretinoin Dosage	Main Findings According to the Abnormal Liver Function Test
Guzman et al., 2016 [33]	Peru	Case report (1)	40 mg/d for 3 months	At baseline, ALT and AST levels were 28 U/L. After 3 months, AST rose to 756 U/L, ALT to 1199 U/L, and alkaline phosphatase to 114 U/L, with normal bilirubin levels. Serology was negative for viral hepatitis, ANA titers were positive (1:160), and IgG levels were elevated. A liver biopsy confirmed autoimmune hepatitis. Prednisone (40 mg/d) was initiated 1 week after stopping isotretinoin, resulting in improved lab values.
Hansen et al., 2016 [94]	USA	Retrospective study (515)	The mean cumulative dose was 8230 mg (range: 800–20,400 mg).	Elevated liver transaminases were infrequent and did not significantly differ from baseline detection rates (1.9% vs. 1.6% at baseline). ALT elevations occurred during 19 (3.3%) courses of isotretinoin treatment. The most severe transaminitis was observed 2 months into treatment in a male patient who had recently started a new vitamin supplement, with ALT levels peaking at 264 U/L. Following the discontinuation of the supplement and halving the isotretinoin dose, ALT levels normalized within a month.
Lee et al., 2016 [52]	NA	Systematic review and meta-analysis (1574)	≥0.5 mg/kg for at least 4 weeks	Most studies reported no significant elevations in liver function tests during isotretinoin treatment. The mean AST value was 22.67 U/L (99% CI, 19.94–25.41 U/L), with a mean difference of 3.72 U/L (99% CI, 2.44–5.01 U/L) at 6.6 weeks. Similarly, the mean ALT value was 21.77 U/L (99% CI, 18.96–24.59 U/L), with a mean difference of 3.22 U/L (99% CI, 0.99–5.45 U/L) at 6.5 weeks.
Tabanlioğlu et al., 2016 [95]	Turkey	Prospective study (70)	The cumulative dose of 150 mg/kg	ALT levels (U/L) increased from a median of 15 (range: 10–38) at baseline to a maximum of 19 (range: 12–93) during treatment ($p = 0.0001$). AST levels (U/L) rose from a median of 19 (range: 11–41) to 24 (range: 16–107) ($p = 0.0001$). GGT levels (U/L) also increased from a median of 15.5 (range: 7–61) to 20.5 (range: 11–77) ($p = 0.0001$).
Ahmad et al., 2015 [96]	Egypt	Randomized controlled trial (58)	The median cumulative dose of 126.1 mg/kg	AST and ALT levels were normal in all patients prior to treatment but significantly increased in the majority during treatment ($p = 0.01$ and $p = 0.008$, respectively). An increase above normal was observed in 3.5% (2 patients) for AST and 12% (7 patients) for ALT, with all elevations limited to Grade 1.

Table A1. *Cont.*

Authors, Year	Country	Study Design (*n*)	Isotretinoin Dosage	Main Findings According to the Abnormal Liver Function Test
Fernández-Crehuet et al., 2014 [97]	Spain	Prospective study (37)	0.5–0.8 mg/kg for 20 weeks	At the 10- and 20-week follow-ups, bilirubin levels were significantly higher in the study group compared with those in controls. At 10 weeks, bilirubin levels were 1.03 ± 0.18 versus 0.52 ± 0.27 in controls ($p < 0.001$), and at 20 weeks, they were 1.38 ± 0.54 versus 0.48 ± 0.26 in controls ($p < 0.001$). Baseline bilirubin levels were also elevated in the study group (1.78 ± 0.65) compared with those in controls (0.50 ± 0.22, $p < 0.001$). ALT levels at 10 weeks were significantly higher in the study group (21.1 ± 7.9) compared with those in controls (15.8 ± 6.6, $p < 0.05$). By 20 weeks, ALT levels decreased, showing no significant difference from controls ($p = 0.25$). No significant differences were observed in AST and GGT levels between the study and control groups at any time point.
Kızılyel et al., 2014 [98]	Turkey	Retrospective study (349)	0.5–1 mg/kg/d for 6 months	Elevated AST levels (≥40 U/L) were observed in 0.9% of patients at 3 months and 1.2% at 6 months, with no significant changes compared to baseline ($p = 0.64$). Similarly, elevated ALT levels (≥40 U/L) were found in 3.4% of patients at both 3 and 6 months, also showing no significant changes from baseline ($p = 0.54$).
Blasiak et al., 2013 [35]	USA	Prospective study (116)	Participants were divided into two groups based on their cumulative dose: those receiving <220 mg/kg and those receiving >220 mg/kg	At a cumulative dose of <220 mg/kg, no abnormalities in AST or ALT levels were observed. However, at a cumulative dose of ≥220 mg/kg, 6.4% of participants had abnormal AST levels, and 1.3% had abnormal ALT levels.
Cyrulnik et al., 2012 [19]	USA	Retrospective study (80)	The cumulative total dose of 290.1 mg/kg	Elevated liver function tests accounted for the largest proportion of abnormalities, observed in 18 patients (22.5%). Among these, ALT Grade 1 elevations (41–100 U/L) were found in 18.8% of patients, while no cases of Grade 2 elevations (101–200 U/L) were reported.
Vieira et al., 2012 [99]	Brazil	Retrospective study (130)	The mean daily dose of isotretinoin was 41.43 ± 10.53 mg, with a treatment duration ranging from 4 to 12 months. The mean body weight of the patients was 63.3 kg.	The mean baseline AST level was 20.44 ± 6.25 U/L, which increased to 24.38 ± 11.9 U/L after three months or more of treatment, showing a mean increase of 3.93 U/L ($p = 0.014$). The mean ALT level increased from 18.24 ± 8.31 U/L at baseline to 23.34 ± 20.02 U/L after three months or more of treatment, with a mean increase of 5.10 U/L ($p = 0.047$). Abnormal AST levels rose from 0% to 8.6% ($p = 1.0$), while abnormal ALT levels increased from 1.4% to 7.1% ($p = 0.780$).

Table A1. *Cont.*

Authors, Year	Country	Study Design (*n*)	Isotretinoin Dosage	Main Findings According to the Abnormal Liver Function Test
Rademaker et al., 2010 [51]	New Zealand	Retrospective study (1743)	The majority of patients received a dosage of 1 mg/kg/d, with a cumulative dose ranging from 150 to 160 mg/kg	Significantly abnormal liver function tests were reported in 20 patients (1.1%).
Chanson et al., 2008 [100]	France	Prospective study (40)	A daily dose of 30 mg was administered for body weight < 70 kg, and 35 mg for body weight ≥ 70 kg, over a period of 28 d.	No differences were observed in AST or ALT levels before and after treatment. However, significant changes were noted in GGT levels, with 14.3% of patients showing elevations.
Amichai et al., 2006 [101]	Israel	Prospective study (638)	0.3–0.4 mg/kg/d for 6 months	A slight, transient elevation of liver enzymes (less than twice the upper limit of normal) was observed in 4.8% of patients.
Ertam I et al., 2006 [102]	Turkey	Prospective study (91)	The mean cumulative dose of 6238 ± 892 mg	Elevated liver enzymes were observed in 20% of patients. However, there were no statistically significant changes in AST ($p = 0.057$) or ALT ($p = 0.737$).
Zane et al., 2006 [50]	USA	Retrospective study (13,772)	65 mg/d with a cumulative dose of 9 g	AST or ALT levels were categorized into four grades based on severity. Grade 1 elevations (41–100 U/L) were observed in 1004 patients (9.8%), while Grade 2 levels (101–200 U/L) were noted in 89 patients (0.9%). Grade 3 elevations (201–800 U/L) occurred in 13 patients (0.1%), and Grade 4 elevations (>800 U/L) were seen in only one patient (0.01%).
Ahmed et al., 2005 [103]	Pakistan	Prospective study (78)	0.5 mg/kg/day	Impaired liver function tests, including elevated transaminases and alkaline phosphatase, were observed in 3 patients (3.8%) after two months of therapy. However, these abnormalities did not necessitate discontinuation of the treatment.

Note: ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CI, confidence interval; d, day(s); GGT, gamma-glutamyl transferase; HR, hazard ratio; IgG, immunoglobulin G; kg, kilogram(s); mg, milligram(s); mg/dL, milligrams per deciliter; NA, not applicable; µmol/L, micromoles per liter; U/L, units per liter; USA, the United States of America.

References

1. Saurat, J.-H.; Halioua, B.; Baissac, C.; Cullell, N.P.; Ben Hayoun, Y.; Aroman, M.S.; Taieb, C.; Skayem, C. Epidemiology of acne and rosacea: A worldwide global study. *J. Am. Acad. Dermatol.* **2024**, *90*, 1016–1018. [CrossRef] [PubMed]
2. Kirsten, N.; Mohr, N.; Augustin, M. Prevalence and cutaneous comorbidity of acne vulgaris in the working population. *Clin. Cosmet. Investig. Dermatol.* **2021**, *14*, 1393–1400. [CrossRef]
3. Dreno, B.; Shourick, J.; Kerob, D.; Bouloc, A.; Taïeb, C. The role of exposome in acne: Results from an international patient survey. *J. Eur. Acad. Dermatol. Venereol.* **2020**, *34*, 1057–1064. [CrossRef] [PubMed]
4. Heng, A.H.S.; Chew, F.T. Systematic review of the epidemiology of acne vulgaris. *Sci. Rep.* **2020**, *10*, 5754. [CrossRef]
5. Cruz, S.; Vecerek, N.; Elbuluk, N. Targeting Inflammation in Acne: Current Treatments and Future Prospects. *Am. J. Clin. Dermatol.* **2023**, *24*, 681–694. [CrossRef] [PubMed]

6. Kurokawa, I.; Layton, A.M.; Ogawa, R. Updated Treatment for Acne: Targeted Therapy Based on Pathogenesis. *Dermatol. Ther.* **2021**, *11*, 1129–1139. [CrossRef]
7. Villani, A.; Nastro, F.; Di Vico, F.; Fabbrocini, G.; Annunziata, M.C.; Genco, L. Oral isotretinoin for acne: A complete overview. *Expert. Opin. Drug Saf.* **2022**, *21*, 1027–1037. [CrossRef]
8. Cho, S.I.; Yang, J.H.; Suh, D.H. Analysis of trends and status of physician-based evaluation methods in acne vulgaris from 2000 to 2019. *J. Dermatol.* **2021**, *48*, 42–48. [CrossRef] [PubMed]
9. Reynolds, R.V.; Yeung, H.; Cheng, C.E.; Cook-Bolden, F.; Desai, S.R.; Druby, K.M.; Freeman, E.E.; Keri, J.E.; Stein Gold, L.F.; Tan, J.K.L.; et al. Guidelines of care for the management of acne vulgaris. *J. Am. Acad. Dermatol.* **2024**, *90*, e1001–e1006. [CrossRef]
10. Paichitrojjana, A.; Paichitrojjana, A. Oral Isotretinoin and Its Uses in Dermatology: A Review. *Drug Des. Dev. Ther.* **2023**, *17*, 2573–2591. [CrossRef]
11. Adelman, M.J.; Sivesind, T.E.; Weber, I.; Bosma, G.; Hochheimer, C.; Karimkhani, C.; Schilling, L.M.; Barbieri, J.S.; Dellavalle, R.P. Prescribing Patterns of Oral Antibiotics and Isotretinoin for Acne in a Colorado Hospital System: Retrospective Cohort Study. *JMIR Dermatol.* **2023**, *6*, e42883. [CrossRef]
12. Alshammari, S.A.; Alamri, Y.; Alanazi, A.M.; Almuhanna, S.A.; Pinjabi, L.; Alsnaidi, N.A. Prevalence and associated risk factors of acne relapse among Saudi acne vulgaris patients using isotretinoin. *Saudi Pharm. J.* **2020**, *28*, 374–379. [CrossRef]
13. Tan, J.; Knezevic, S.; Boyal, S.; Waterman, B.; Janik, T. Evaluation of evidence for acne remission with oral isotretinoin cumulative dosing of 120–150 mg/kg. *J. Cutan. Med. Surg.* **2016**, *20*, 13–20. [CrossRef] [PubMed]
14. Banderowicz, P.; Roszyk, A.; Wierzbowska, N.; Rodak, M. The effect of isotretinoin therapy on the circulatory system. *Forum Dermatol.* **2024**, *10*, 10–17. [CrossRef]
15. Bruno, C.D.; Harmatz, J.S.; Duan, S.X.; Zhang, Q.; Chow, C.R.; Greenblatt, D.J. Effect of lipophilicity on drug distribution and elimination: Influence of obesity. *Br. J. Clin. Pharmacol.* **2021**, *87*, 3197–3205. [CrossRef] [PubMed]
16. U.S. Food and Drug Administration. Label for [Drug Name], Reference ID: 018662s059. 2008. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/018662s059lbl.pdf (accessed on 6 December 2024).
17. U.S. Food and Drug Administration. Label for [Drug Name], Reference ID: 021951s013. 2009. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021951s013lbl.pdf (accessed on 6 December 2024).
18. Khismatulina, I.M.; Faizullina, E.V. Retrospective analysis of the results of systemic therapy of moderate to severe papulo-pustular acne. *Vestn. Dermatol. I Venerol.* **2023**, *99*, 103–111. [CrossRef]
19. Cyrulnik, A.A.; Viola, K.V.; Gewirtzman, A.J.; Cohen, S.R. High-dose isotretinoin in acne vulgaris: Improved treatment outcomes and quality of life. *Int. J. Dermatol.* **2012**, *51*, 1123–1130. [CrossRef]
20. Mobacken, H. Treatment with low-dose isotretinoin is effective for patients with moderate inflammatory acne. *Lakartidningen* **2021**, *118*, 21117.
21. Sadeghzadeh-Bazargan, A.; Ghassemi, M.; Goodarzi, A.; Roohaninasab, M.; Najar Nobari, N.; Behrangi, E. Systematic review of low-dose isotretinoin for treatment of acne vulgaris: Focus on indication, dosage, regimen, efficacy, safety, satisfaction, and follow up, based on clinical studies. *Dermatol. Ther.* **2021**, *34*, 14438. [CrossRef] [PubMed]
22. Cumurcu, T.; Sezer, E.; Kilic, R.; Bulut, Y. Comparison of dose-related ocular side effects during systemic isotretinoin administration. *Eur. J. Ophthalmol.* **2009**, *19*, 196–200. [CrossRef] [PubMed]
23. Fallah, H.; Rademaker, M. Isotretinoin for acne vulgaris–an update on adverse effects and laboratory monitoring. *J. Dermatol. Treat.* **2022**, *33*, 2414–2424. [CrossRef] [PubMed]
24. Emtenani, S.; Abdelghaffar, M.; Ludwig, R.J.; Schmidt, E.; Kridin, K. Risk and timing of isotretinoin-related laboratory disturbances: A population-based study. *Int. J. Dermatol.* **2024**, *63*, 1740–1747. [CrossRef] [PubMed]
25. Al-Hawamdeh, M.I.; Al-Ameri, M.; Lutfi, S.; Muhtaseb, N.; Takhayneh, R.; Awamreh, T. Knowledge, Attitude, and Risk Perception in Oral Isotretinoin Use: A Cross-Sectional Study from Jordan. *Dermatol. Res. Pract.* **2024**, *2024*, 7714527. [CrossRef]
26. Hosseinpour, P.; Gholamabbas, G.; Pezeshkian, F.; Erfani, A.; Shahriarirad, R.; Parhizkar, A.R. Practice and attitude of general practitioners towards initiating isotretinoin for acne vulgaris in Fars province, Iran: Cross-sectional study. *BMC Prim. Care* **2024**, *25*, 27. [CrossRef]
27. Carmody, K.; Rouse, M.; Nolan, D.; Quinlan, D. GPs' practice and attitudes to initiating isotretinoin for acne vulgaris in Ireland: A cross-sectional questionnaire survey in primary care. *Br. J. Gen. Pract.* **2020**, *70*, e651–e656. [CrossRef] [PubMed]
28. Hobson, J.G.; Cunningham, M.J.; Lesiak, K.; Lester, E.B.; Tegeder, A.R.; Zeeck, E.; Hugh, J.M.; Lin, J.H. Isotretinoin monitoring trends: A national survey of dermatologists. *J. Drugs Dermatol.* **2017**, *16*, 557–564. [PubMed]
29. Barbieri, J.S.; Shin, D.B.; Wang, S.; Margolis, D.J.; Takeshita, J. The clinical utility of laboratory monitoring during isotretinoin therapy for acne and changes to monitoring practices over time. *J. Am. Acad. Dermatol.* **2020**, *82*, 72–79. [CrossRef]
30. Garcia-Cortes, M.; Robles-Diaz, M.; Stephens, C.; Ortega-Alonso, A.; Lucena, M.I.; Andrade, R.J. Drug induced liver injury: An update. *Arch. Toxicol.* **2020**, *94*, 3381–3407. [CrossRef] [PubMed]
31. Lee, K.W.A.; Chan, L.K.W.; Lee, C.H.; Wan, J.; Yi, K.-H. Idiosyncratic Reaction of Isotretinoin: A Review. *Dermatol. Rev.* **2024**, *5*, e70001. [CrossRef]

32. Varol, F.I.; Selimoglu, M.A.; Karadag, N.; Gungor, S. Isotretinoin Hepatotoxicity or Isotretinoin Induced Autoimmune Hepatitis? *Indian. J. Paediatr. Dermatol.* **2021**, *22*, 70–72. [CrossRef]
33. Guzman Rojas, P.; Gallegos Lopez, R.; Ciliotta Chehade, A.; Scavino, Y.; Morales, A.; Tagle, M. Autoimmune hepatitis induced by isotretionine. *Rev. De Gastroenterol. Del Peru Organo Of. De La Soc. De Gastroenterol. Del Peru* **2016**, *36*, 86–89.
34. Öktem, A.; Hayran, Y.; Arı, E.; Yalçın, B. Minimize the regular laboratory monitoring during the systemic isotretinoin treatment: Data of 704 patients with acne vulgaris. *J. Dermatolog Treat.* **2019**, *30*, 813–817. [CrossRef] [PubMed]
35. Blasiak, R.C.; Stamey, C.R.; Burkhart, C.N.; Lugo-Somolinos, A.; Morrell, D.S. High-dose isotretinoin treatment and the rate of retrial, relapse, and adverse effects in patients with acne vulgaris. *JAMA Dermatol.* **2013**, *149*, 1392–1398. [CrossRef]
36. Yaqoubi, W.; Touby, S.; Hossain, M.A. Laboratory investigations of liver function and lipid profiles tests before and after oral isotretinoin treatment among Acne valgaris clients at Ibri Polyclinic: A retrospective study. *Toxicol. Rep.* **2024**, *13*, 101799. [CrossRef] [PubMed]
37. Alajaji, A.; Alrawaf, F.A.; Alosayli, S.I.; Alqifari, H.N.; Alhabdan, B.M.; Alnasser, M.A. Laboratory abnormalities in acne patients treated with oral isotretinoin: A retrospective epidemiological study. *Cureus* **2021**, *13*, e19031. [CrossRef]
38. Abd-Elaziz, E.; El-Kamshoushy, A.-E.; Sherif, A.; Wahdan, I. Oral Isotretinoin and its Association with Liver Functions and Cholesterol Level among Acne Patients. *J. High. Inst. Public. Health* **2020**, *50*, 25–31. [CrossRef]
39. Özaslan, M.; Peker, D. Evaluation of Laboratory Follow-up in Acne Patients Treated With Isotretinoin. *Cutis* **2023**, *112*, 38–43. [CrossRef]
40. Hussain, M.; Fatima, M.; Shaukat, S.; Barkat, M.Q.; Alqahtani, T.; Alqahtani, A.M.; Mei, L.; Shi, W.; Wu, X. Drug-metabolizing enzymes and oxidative stress. In *Biochemistry of Drug Metabolizing Enzymes: Trends and Challenges*; Academic Press: Cambridge, MA, USA, 2022; pp. 521–544. [CrossRef]
41. McGill, M.R.; Jaeschke, H. Oxidant stress, antioxidant defense, and liver injury. In *Drug-Induced Liver Disease*; Academic Press: Cambridge, MA, USA, 2013; pp. 71–84. [CrossRef]
42. Allameh, A.; Niayesh-Mehr, R.; Aliarab, A.; Sebastiani, G.; Pantopoulos, K. Oxidative Stress in Liver Pathophysiology and Disease. *Antioxidants* **2023**, *12*, 1653. [CrossRef]
43. Daye, M.; Belviranli, M.; Okudan, N.; Mevlitoglu, I.; Oz, M. The effect of isotretinoin therapy on oxidative damage in rats. *Dermatol. Ther.* **2020**, *33*, e14111. [CrossRef]
44. Xu, C.X. Prevention of Isotretinoin-Induced Oxidative Stress and Hepatotoxicity. *MATEC Web Conf.* **2024**, *404*, 04005.
45. Georgala, S.; Papassotiriou, I.; Georgala, C.; Demetriou, E.; Schulpis, K.H. Isotretinoin therapy induces DNA oxidative damage. *Clin. Chem. Lab. Med.* **2005**, *43*, 1178–1182. [CrossRef] [PubMed]
46. Erturan, İ.; Naziroğlu, M.; Akkaya, V.B. Isotretinoin treatment induces oxidative toxicity in blood of patients with acne vulgaris: A clinical pilot study. *Cell Biochem. Funct.* **2012**, *30*, 552–557. [CrossRef] [PubMed]
47. Ozkol, H.U.; Ozkol, H.; Karadag, A.S.; Bilgili, S.G.; Tuluce, Y.; Calka, O. Oral isotretinoin therapy of acne patients decreases serum paraoxonase-1 activity through increasing oxidative stress. *Drug Chem. Toxicol.* **2015**, *38*, 63–66. [CrossRef] [PubMed]
48. Alzoubi, K.H.; Khabour, O.F.; Hassan, R.E.; Qarqaz, F.; Al-Azzam, S.; Mhaidat, N. The effect of genetic polymorphisms of RARA gene on the adverse effects profile of isotretinoin-treated acne patients. *Int. J. Clin. Pharmacol. Ther.* **2013**, *51*, 631–640. [CrossRef]
49. Vallerand, I.A.; Lewinson, R.T.; Farris, M.S.; Sibley, C.D.; Ramien, M.L.; Bulloch, A.G.M.; Patten, S.B. Efficacy and adverse events of oral isotretinoin for acne: A systematic review. *Br. J. Dermatol.* **2018**, *178*, 76–85. [CrossRef]
50. Zane, L.T.; Leyden, W.A.; Marqueling, A.L.; Manos, M.M. A population-based analysis of laboratory abnormalities during isotretinoin therapy for acne vulgaris. *Arch. Dermatol.* **2006**, *142*, 1016–1022. [CrossRef] [PubMed]
51. Rademaker, M. Adverse effects of isotretinoin: A retrospective review of 1743 patients started on isotretinoin. *Australas. J. Dermatol.* **2010**, *51*, 248–253. [CrossRef] [PubMed]
52. Lee, Y.H.; Scharnitz, T.P.; Muscat, J.; Chen, A.; Gupta-Elera, G.; Kirby, J.S. Laboratory Monitoring During Isotretinoin Therapy for Acne: A Systematic Review and Meta-analysis. *JAMA Dermatol.* **2016**, *152*, 35–44. [CrossRef] [PubMed]
53. Brzezinski, P.; Borowska, K.; Chiriac, A.; Smigielski, J. Adverse effects of isotretinoin: A large, retrospective review. *Dermatol. Ther.* **2017**, *30*, 12483. [CrossRef]
54. National Center Institute. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 2017. Available online: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm (accessed on 4 December 2024).
55. Sauder, M.B.; Cheung, L.; Beecker, J. Acitretin-induced hepatitis: When to monitor Cholestatic enzymes. *J. Cutan. Med. Surg.* **2015**, *19*, 115–120. [CrossRef] [PubMed]
56. Xia, E.; Han, J.; Faletsky, A.; Baldwin, H.; Beleznay, K.; Bettoli, V.; Dréno, B.; Goh, C.L.; Stein Gold, L.; Gollnick, H.; et al. Isotretinoin Laboratory Monitoring in Acne Treatment: A Delphi Consensus Study. *JAMA Dermatol.* **2022**, *158*, 942–948. [CrossRef] [PubMed]
57. Chinnappan, R.; Mir, T.A.; Alsalameh, S.; Makhzoum, T.; Alzhrani, A.; Al-Kattan, K.; Yaqinuddin, A. Low-Cost Point-of-Care Monitoring of ALT and AST Is Promising for Faster Decision Making and Diagnosis of Acute Liver Injury. *Diagnostics* **2023**, *13*, 2967. [CrossRef]

58. Ivica, J.; Hill, S. The potential of reducing AST testing in hospital settings. *Clin. Biochem.* **2019**, *64*, 57–59. [CrossRef] [PubMed]
59. Pollock, N.R.; Rolland, J.P.; Kumar, S.; Beattie, P.D.; Jain, S.; Noubary, F.; Wong, V.L.; Pohlmann, R.A.; Ryan, U.S.; Whitesides, G.M. A paper-based multiplexed transaminase test for low-cost, point-of-care liver function testing. *Sci. Transl. Med.* **2012**, *4*, 152ra129. [CrossRef] [PubMed]
60. Tosun, M. Effect of isotretinoin use on hematological parameters and biochemical values. *Ann. Clin. Anal. Med.* **2022**, *13*, 4328. [CrossRef]
61. Soutou, B.; Sleiman, J.; Tomb, R.; Kechichian, E.; Helou, J. Prevalence of adverse events varies with the different oral isotretinoin brands in acne treatment: A retrospective observational study. *Arch. Dermatol. Res.* **2023**, *315*, 1533–1539. [CrossRef] [PubMed]
62. Pona, A.; Cardenas-de la Garza, J.A.; Haidari, W.; Cline, A.; Feldman, S.R.; Taylor, S.L. Abnormal liver function tests in acne patients receiving isotretinoin. *J. Dermatolog. Treat.* **2021**, *32*, 469–472. [CrossRef] [PubMed]
63. Backman, J.T.; Filppula, A.M.; Niemi, M.; Neuvonen, P.J. Role of cytochrome P450 2C8 in drug metabolism and interactions. *Pharmacol. Rev.* **2016**, *68*, 168–241.
64. Zhou, S.F.; Zhou, Z.W.; Yang, L.P.; Cai, J.P. Substrates, inducers, inhibitors and structure-activity relationships of human cytochrome P450 2C9 and implications in drug development. *Curr. Med. Chem.* **2009**, *16*, 3480–3675. [CrossRef] [PubMed]
65. Zhou, S.-F. Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. *Curr. Drug Metab.* **2008**, *9*, 310–322. [CrossRef]
66. Fahmi, O.A.; Shebley, M.; Palamanda, J.; Sinz, M.W.; Ramsden, D.; Einolf, H.J.; Chen, L.; Wang, H. Evaluation of CYP2B6 induction and prediction of clinical drug–drug interactions: Considerations from the IQ consortium induction working group—An industry perspective. *Drug Metab. Dispos.* **2016**, *44*, 1720–1730. [CrossRef] [PubMed]
67. Rowbotham, S.E.; Illingworth, N.A.; Daly, A.K.; Veal, G.J.; Boddy, A.V. Role of UDP-glucuronosyltransferase isoforms in 13-cis retinoic acid metabolism in humans. *Drug Metab. Dispos.* **2010**, *38*, 1211–1217. [CrossRef] [PubMed]
68. Nuriyeva, N.; Yurdgulu, E.E.; Albayrak, A.; Aliyev, H.; Aliyeva, K.; Erkayman, B.; Bayir, Y. Evaluation of the protective effects of curcumin-rich turmeric (*Curcuma longa*) extract against isotretinoin-induced liver damage in rats. *Toxicol. Mech. Methods* **2024**, *34*, 122–129. [CrossRef] [PubMed]
69. Taziki, S.; Gholamzadeh, F.; Hosseini, R. The hepatoprotective effects of taurine against oxidative stress induced by isotretinoin in rats. *J. Biochem. Mol. Toxicol.* **2022**, *36*, e23178. [CrossRef]
70. Saied, N.M.; Hamza, A.A. Selenium ameliorates isotretinoin-induced liver injury and dyslipidemia via antioxidant effect in rats. *Toxicol. Mech. Methods* **2014**, *24*, 433–437. [CrossRef] [PubMed]
71. Tawfiq, P.; Sharef, T.Y.; Ali, K.A.; Salih, L.S. Effect of Isotretinion on Rat's Liver and Aptness of Cumin Oil in Protection. *Diyala J. Med.* **2020**, *18*, 32–43. [CrossRef]
72. Kus, S.; Gün, D.; Demirçay, Z.; Sur, H. Vitamin E does not reduce the side-effects of isotretinoin in the treatment of acne vulgaris. *Int. J. Dermatol.* **2005**, *44*, 248–251. [CrossRef]
73. Dara, L.; Hewett, J.; Lim, J.K. Hydroxycut hepatotoxicity: A case series and review of liver toxicity from herbal weight loss supplements. *World J. Gastroenterol.* **2008**, *14*, 6999–7004. [CrossRef]
74. DeKlotz, C.M.C.; Roby, K.D.; Friedlander, S.F. Dietary supplements, isotretinoin, and liver toxicity in adolescents: A retrospective case series. *Pediatrics* **2017**, *140*, e20152940. [CrossRef] [PubMed]
75. Timcheh-Hariri, A.; Balali-Mood, M.; Aryan, E.; Sadeghi, M.; Riahi-Zanjani, B. Toxic hepatitis in a group of 20 male body-builders taking dietary supplements. *Food Chem. Toxicol.* **2012**, *50*, 3826–3832. [CrossRef] [PubMed]
76. Dancygier, H. Drug- and toxin-induced liver injury. In *Clinical Hepatology*; Springer: Berlin/Heidelberg, Germany, 2010; Volume 2, pp. 1223–1231.
77. Elgharably, N.; Abadie, M.A.; Al Abadie, M.; Ball, P.A.; Morrissey, H. Vitamin B group levels and supplementations in dermatology. *Dermatol. Rep.* **2023**, *15*, 9511. [CrossRef]
78. Duffy, E.K.; Bales, C.B.; Carlow, D.C.; Treat, J.R. Spurious elevation of aspartate aminotransferase in a patient on isotretinoin. *J. Am. Acad. Dermatol.* **2014**, *71*, e132–e133. [CrossRef] [PubMed]
79. Alrasheed, A.A.; Alsadhan, K.F.; Alfawzan, N.F.; AbuDujain, N.M.; Alnasser, A.H.; Almousa, H. Impact of Isotretinoin on Blood Lipids and Liver Enzymes: A Retrospective Cohort Study in Saudi Arabia. *Ther. Clin. Risk Manag.* **2024**, *20*, 567–575. [CrossRef] [PubMed]
80. Li, Y.; Zeng, Y.; Chen, Z.; Nie, S.; Wu, Z. The efficiency and safety of low-dosage isotretinoin therapy for Chinese acne vulgaris patients. *J. Cosmet. Dermatol.* **2024**, *23*, 926–930. [CrossRef] [PubMed]
81. Maden, S. Alterations in Alanine Transaminase, Aspartate Transaminase, Gamma-Glutamyl Transpeptidase, and Creatine Kinase in Acne Patients Undergoing Isotretinoin Treatment: A Retrospective Evaluation of Laboratory Tests. *Cureus* **2024**, *16*, e57296. [CrossRef]
82. Al Dhafiri, M.; Kaliyadan, F.; Almukhaimar, S.; Alsultan, F.; Al Hayim, E.; Alnaim, R.; Aldossari, A. Isotretinoin Use and Liver Enzymes Changes: A Single-Center Study in Saudi Arabia. *Cureus* **2023**, *15*, e51263. [CrossRef] [PubMed]

83. Parthasarathy, V.; Shah, N.; Kirkorian, A.Y. The utility of laboratory testing for pediatric patients undergoing isotretinoin treatment. *Pediatr. Dermatol.* **2022**, *39*, 731–733. [CrossRef]
84. Al-Haddab, M.; Alhuqayl, A.; Alsharif, H.; Alolyet, D.; Altaleb, R. Results of Laboratory Monitoring in Patients Taking Isotretinoin for Acne. *Cutis* **2021**, *108*, 43–45. [CrossRef] [PubMed]
85. Shah, R.; Kroshinsky, D. Re-evaluating the need for routine laboratory monitoring in patients taking isotretinoin: A retrospective analysis. *J. Am. Acad. Dermatol.* **2021**, *85*, 504–506. [CrossRef]
86. Akouch, H.; Bouhairie, M.M.; Nasreddine, S. Case Report of Acute Liver Failure Induced By Isotretinoin Medication. *J. Gastroenterol. Hepatol. Rep.* **2021**, *2*, 1–5. [CrossRef]
87. Acar, Ş.; Yazar, Ş.; Kargı, A.; Dönmez, R.; Aslan, S.; Polat, K.Y.; Arıkan, Ç.; Akyıldız, M. A Case of Living Donor Liver Transplantation due to Hepatic Failure Cause of Isotretinoin Therapy. *J. Turk. Acad. Dermatol.* **2020**, *14*, 57–60. [CrossRef]
88. Tkachenko, E.; Sharma, P.; Mostaghimi, A. Abnormal Baseline Lab Results Rarely Lead to Treatment Modification for Patients on Isotretinoin. *Dermatology* **2020**, *236*, 517–520. [CrossRef] [PubMed]
89. Aktas, H.; Ertugrul, G.; Parlak, M.; Unal, M. Long-term isotretinoin use does not cause parenchymal liver change: Ultrasonographic study in 50 patients. *Dermatol. Ther.* **2019**, *32*, e13012. [CrossRef] [PubMed]
90. Nazarian, R.S.; Zheng, E.; Halverstam, C.; Cohen, S.R.; Wolkoff, A.W. Prolonged Serum Alanine Aminotransferase Elevation Associated with Isotretinoin Administration. *Case Rep. Hepatol.* **2019**, *2019*, 9270827. [CrossRef] [PubMed]
91. Webster, G.F.; Webster, T.G.; Grimes, L.R. Laboratory tests in patients treated with isotretinoin: Occurrence of liver and muscle abnormalities and failure of AST and ALT to predict liver abnormality. *Dermatol. Online J.* **2017**, *23*, 5. [CrossRef]
92. Yap, F.B. Safety and efficacy of fixed-dose 10 mg daily isotretinoin treatment for acne vulgaris in Malaysia. *J. Cosmet. Dermatol.* **2017**, *16*, 348–352. [CrossRef]
93. Bugdayci, G.; Polat, M.; Oguzman, H.; Cinpolat, H.Y. Interpretation of Biochemical Tests Using the Reference Change Value in Monitoring Adverse Effects of Oral Isotretinoin in 102 Ethnic Turkish Patients. *Lab. Med.* **2016**, *47*, 213–219. [CrossRef]
94. Hansen, T.J.; Lucking, S.; Miller, J.J.; Kirby, J.S.; Thiboutot, D.M.; Zaenglein, A.L. Standardized laboratory monitoring with use of isotretinoin in acne. *J. Am. Acad. Dermatol.* **2016**, *75*, 323–328. [CrossRef]
95. Tabanlioğlu Onan, D.; Hazar Tantoğlu, B.; Alli, N.; Özkan, S.; Samsar, U.; Köseoğlu, H.T.; Artüz, R.F. Evaluation of the gastrointestinal findings of nodulocystic acnepatients during systemic isotretinoin therapy. *Turk. J. Med. Sci.* **2016**, *46*, 820–824. [CrossRef]
96. Ahmad, H.M. Analysis of clinical efficacy, side effects, and laboratory changes among patients with acne vulgaris receiving single versus twice daily dose of oral isotretinoin. *Dermatol. Ther.* **2015**, *28*, 151–157. [CrossRef]
97. Fernández-Crehuet, P.; Fernández-Crehuet, J.L.; Allam, M.F.; Fernández-Crehuet Navajas, R. Hepatotoxicity of isotretinoin in patients with acne and Gilbert's syndrome: A comparative study. *BMJ Open* **2014**, *4*, e004441. [CrossRef]
98. Kızılyel, O.; Metin, M.S.; Elmas, Ö.F.; Çayır, Y.; Aktaş, A. Effects of oral isotretinoin on lipids and liver enzymes in acne patients. *Cutis* **2014**, *94*, 234–238.
99. Vieira, A.S.; Beijamini, V.; Melchiors, A.C. The effect of isotretinoin on triglycerides and liver aminotransferases. *An. Bras. Dermatol.* **2012**, *87*, 382–387. [CrossRef] [PubMed]
100. Chanson, A.; Cardinault, N.; Rock, E.; Martin, J.F.; Souteyrand, P.; D'Incan, M.; Brachet, P. Decreased plasma folate concentration in young and elderly healthy subjects after a short-term supplementation with isotretinoin. *J. Eur. Acad. Dermatol. Venereol.* **2008**, *22*, 94–100. [CrossRef]
101. Amichai, B.; Shemer, A.; Grunwald, M.H. Low-dose isotretinoin in the treatment of acne vulgaris. *J. Am. Acad. Dermatol.* **2006**, *54*, 644–646. [CrossRef] [PubMed]
102. Ertam, I.; Alper, S.; Unal, I. Is it necessary to have routine blood tests in patients treated with isotretinoin? *J. Dermatolog Treat.* **2006**, *17*, 214–216. [CrossRef] [PubMed]
103. Ahmed, I.; Wahid, Z.; Nasreen, S. Adverse effects of systemic isotretinoin therapy: A study of 78 patients. *J. Pak. Assoc. Dermatol.* **2005**, *15*, 242–246.