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Status Report on Oral Isotretinoin in the Management of Acne Vulgaris: Why All the Discussion about Drug Absorption and Relapse Rates?

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Abstract Oral isotretinoin is a highly successful therapy for severe, refractory inflammatory acne vulgaris (AV) that is indicated especially for patients with multiple nodulocystic lesions. After over 30 years of clinical use, it is apparent that the majority of patients experience clearing of AV with prolonged remission after a course of oral isotretinoin therapy is completed. Multiple reports have shown that recurrence of AV occurs in some patients and is more likely in those who had not achieved adequate cumulative exposure to a total dose of drug, which has been defined as 120 – 150-mg/kg. As the pharmacokinetic profile of orally administered isotretinoin shows that gastrointestinal absorption is highly dependent on administration with a high calorie-high fat meal, it is has been considered that patients who ingest a conventional formulation of oral isotretinoin without an adequate meal or without food at all may be predisposed to a higher rate and earlier onset of recurrence of AV as their cumulative systemic exposure is effectively reduced by up to 60 %. A new formulation of oral isotretinoin uses a technology where isotretinoin is pre-solubilized in a lipid matrix so absorption is not markedly diminished if the patient does not ingest the drug with an adequate meal. As the data analysis on recurrence of AV in patients treated with conventional formulations of oral isotretinoin are retrospective, additional research and vigilant observation are needed to determine if the new formulation will provide better long term outcomes.

Keywords Oral isotretinoin · Acne vulgaris · Recalcitrant nodular acne · Pharmacokinetic profile

Introduction

Oral isotretinoin (OI) has been available for use in United States (US) for over three decades and has revolutionized the treatment of severe inflammatory acne vulgaris (AV). Unlike other medical therapies for AV which require continued administration to sustain therapeutic benefit, OI is capable of clearing AV and sustaining prolonged remissions in many patients who complete an adequate course of therapy [1–5]. The approved indication for use of OI in the US is "treatment of severe, recalcitrant nodular acne", with "severe" meaning the presence of many nodules, although quantity definitions are not mandated [6, 7]. A plethora of publications support the consistent efficacy of OI in clearing severe cases of AV that present with multiple deep inflammatory and nodulocystic lesions on the face and/or trunk, generally using a daily dose of 0.5 mg/kg to 1 mg/kg over a duration of 15 to 20 weeks, although both higher and lower daily doses have been used with success [3–6, 8–12••, 13–16].

Although the ability to clear cases of severe refractory AV with OI has been well established, the issue that has arisen is what daily dose and/or duration of therapy, or critical level of systemic exposure to OI is needed to sustain prolonged remission and reduce the likelihood of a recurrence of AV that requires retreatment with OI, or a regimen inclusive of a systemic such as an oral antibiotic in combination with a topical regimen [4, 11, 12••, 15–17••]. Several factors have been reported to influence the potential for recurrence of AV that warrants retreatment including early onset of severe nodulocystic/inflammatory AV, underlying endocrinologic disease producing androgen excess (i.e., polycystic ovary syndrome), presence of macrocomedones, and inadequate

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dosing of OI [13–17••, 18–22]. However, inadequate attention has been given to the 63 % decrease in gastrointestinal (GI) absorption of isotretinoin that occurs when OI is administered on an empty stomach as compared to with a high calorie-high fat meal [17••, 23]. As there is evidence that cumulative systemic exposure to OI directly affects the duration of remission, the variability in GI absorption of isotretinoin with and without an adequate meal has been raised as a potential cause for recurrence of AV that warrants aggressive retreatment [12••, 13–17••, 18–25].

Historic Data on Need for Retreatment after Oral Isotretinoin Use

Multiple trials and data analyses have assessed the potential for recurrence of AV and the need for retreatment, including with another course of OI [4, 11, 12••, 14–17••, 18, 20–22, 24, 25]. As different analyses have used various criteria to define recurrence of AV and need for retreatment, it is important to distinguish what is specifically defined depending upon the publication being referenced. Recurrences of AV at some point in time after completion of an initial course of OI may range in severity, are variable with regard to the lesion types that are present (i.e., comedonal, vs. superficial inflammatory vs. nodular), and differ in the type of retreatment used when recurrence of AV was observed (topical therapy only, topical agents in combination with an oral antibiotic, an additional course of OI). Available studies and patient database analyses have noted a wide range of AV recurrence rates. Overall, patients who experienced a recurrence of AV after completion of a course of OI were retreated with topical therapy alone (16 – 21 %), the combination of topical therapy and an oral antibiotic (3.3 – 27 %), or at least one additional course of OI (16 – 23 %) [12••, 15, 17 ••, 18–22, 25]. In addition, the majority of publications that analyze recurrence of AV after treatment with OI included cases that were generally treated with daily doses of 0.5 mg/kg/day to 1.0 mg/kg/day, with some studies including patients treated with lower (0.1 mg – 0.2 mg/kg) or higher (>1 mg – 2 mg/kg) daily doses, with durations of therapy and time course of response also evaluated in most cases. [4, 8–12••, 14–17••, 18–22, 24, 25].

Patients followed over 5 years after completing their initial course of OI required an additional course in 22.7 %, two additional courses in 17 %, and three additional courses in 5 % of cases [21]. A retrospective review of a large managed-care practice database reported that 61 % of AV patients treated with a course of OI later underwent retreatment for AV, with 22.9 % undergoing at least one additional course of OI [22]. An analysis of first time users of OI (N=17,351) over the time period of 1984 – 2003 demonstrated that 41 % experienced a recurrence of AV, with 26 % undergoing an additional course of OI [25].

Outcomes from Data Analyses on Need for Retreatment after Oral Isotretinoin

Retrospective evaluation of collective data from multiple publications and databases have shown that the potential for recurrence of AV after the initial course of treatment with OI correlates with daily dose (mg/kg/day), duration of therapy, and cumulative exposure described as the total dose administered over the course of therapy (total mg/kg) [4, 12••, 13–17••, 18–22, 24, 25]. Among the cases of recurrence of AV after use of OI, the onset of recurrence was as early as 6 months, and usually within 2 to 3 years after completion of OI. The subset of patients who needed at least one additional course of OI usually completed this within 2 to 3 years, of their initial course [1, 4, 12••, 13–17••, 18–25]. Given the same duration of OI therapy which was usually 16 to 20 weeks, a consistent trend for recurrence of AV has been observed in several studies, with a lower daily dose (0.1 – 0.2 mg/kg/day) associated with a higher recurrence rate and often an earlier onset of recurrent AV as compared to higher daily doses (0.5- mg/kg/day; 1 mg/ kg/day) [12••, 13–17••, 18–25]. The culmination of data analysis supports that a course of OI achieves a total dose of 120 – 50 mg/kg to reduce the potential for recurrence of AV (Table 1) [17••, 18–22]. Based on this guideline, if the daily dose of OI is lowered, the duration of therapy then needs to be prolonged.

What Are the Differences in Phramacokinetic Profiles Among the Currently Available Oral Isotretinoin Formulations?

The pharmacokinetic (PK) profile of conventional formulations of OI are based on administration with a high calorie-high fat meal which is the mandated method used during the approval process with the original reference brand of OI

Table 1 Oral isotretinoin - what we learned from 30+ years of experience [6, 17••]

-After several years of clinical experience, higher than anticipated recurrence rates of acne led to analysis of reasons for retreatment
• Cumulative systemic exposure over treatment course identified as a *major factor influencing how often acne retreatment is needed*
-*Target Cumulative Dose* identified: 120 – 150 mg/kg is the generally accepted target treatment goal based on collective data analysis
• Lower daily dose over fixed duration (i.e., 20 weeks) correlated with increased rate and earlier onset of relapse (need for retreatment)
• Ingestion on an empty stomach (unfed) significantly reduces gastrointestinal absorption and may contribute to increased rate and earlier onset of relapse

(Accutane) [17••, 26]. With the exception of the recently introduced OI-Lidose brand formulation (Absorica) which is a distinct formulation with a different PK profile, all of the branded generic formulations of OI (i.e., Claravis, Amnesteen, Zenatane) that are available in the US are based on the PK profile of the original reference brand (Accutane), or a recognized identical formulation now that the original brand of OI is no longer being manufactured [17••]. OI-Lidose is a novel capsule formulation of OI that exhibits a unique PK profile that differs markedly from conventional OI formulations [27]. This formulation includes pre-solubilized isotretinoin in a lipid matrix which allows for less dependency on high fat intake to achieve reasonable GI absorption, although maximal absorption still occurs in the presence of a high fat meal. OI-Lidose ingested on an empty stomach is approximately 80 % absorbed from the GI tract as compared to ingestion with a high calorie-high fat meal, as compared to conventional formulations of OI which are only approximately 40 % absorbed in the fasting state as compared to an adequate fed state [17••, 27].

How Might Dietary Factors Influence the Long Term Response (Recurrence Rate) of Acne Vulgaris After Completion of a Course of Oral Isotretinoin Therapy?

It has been reported that OI is 1.5 to 2 times more bioavailable with food ingested 1 h before, concomitantly with, or 1 h after dosing than when given on an empty stomach (during a complete fast) [23]. To add, peak plasma concentrations between fed (high calorie-high fat meal) and fasted conditions can vary by nearly threefold, which may potentially affect the rate and time of onset of recurrence of AV after completion of a course of OI if the drug is frequently ingested without an adequate meal. It is difficult to quantify how much impact co-ingestion of a conventional OI formulation with or without an adequate meal actually has on the potential for recurrence of AV as the analyses are retrospective at present. Nevertheless, measures to optimize cumulative systemic isotretinoin exposure are rational as lower exposures during a course of therapy have been correlated directly with a higher recurrence rate of AV.

Compliance with Ethics Guidelines

Conflict of Interest JQ Del Rosso is a researcher (R), speaker (S), and/or consultant (S) for several companies that market and/or develop products for acne vulgaris including Allergan (R,S,C), Bayer (R,S,C), Dermira (C), Galderma (R,S,C), Medicis (division of Valeant) (RS,C), Onset Dermatologics (S,C), Promius (S,C), Ranbaxy (S,C), and Warner-Chilcott (S). Both Promius and Ranbaxy market formulations of oral isotretinoin in the United States. He has served as a consultant and speaker for both companies in the areas of acne as a disease state and oral isotretinoin therapy.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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