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Safety and Efficacy of Oral Isotretinoin in the Treatment of Acne Vulgaris

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Abstract

Background: Oral isotretinoin is widely used for acne vulgaris. It is an effective agent but has a wide spectrum of potential side-effects.

A clinical audit was carried out in a tertiary care hospital to determine current practice regarding oral isotretinoin use in acne vulgaris and to evaluate the association between adherence to guidelines and safety and efficacy profile

Material and Methods: The data was obtained from the medical record of patients. It included details like age, gender, weight, duration of acne, method of calculation of severity of acne, history of depression and the scoring system used to assess it, previous treatments used for acne, total duration and dose of isotretinoin, monitoring of laboratory investigations before, during and at the end of treatment, response of the disease and side effect profile. Results were collated and analyzed on SPSS 17 statistical software

Results: 51.8% (207 patients) were female and 48.3% (193patients) were male, with mean age 22.3 +7.2 years. Mean cumulative dose of isotretinoin was 117.31 +- 28.64, with the majority of the patients (81.7%) receiving 80 – 150 mg/kg body weight. 347 (86%) of the patients had an excellent response with complete or near complete clearance of acne; 2 patients (0.5%) had a partial response with mild acne persisting at the time of discontinuation of therapy. 40 patients (10%) were lost to follow up and eleven (2.75%) discontinued treatment due to persistent side effects. Two patients, while on treatment, became pregnant and opted for therapeutic abortions.

Conclusion: Results support the need to adhere to the current guidelines as oral isotretinoin is an effective and well-tolerated drug when used under supervision. Treating physicians need to be vigilant to monitor potential side effects.

Introduction

Oral isotretinoin has been shown to be useful in controlling acne that does not respond to usual treatments with oral antibiotics and that can produce significant physical or emotional scarring. Dosage of isotretinoin varies; in general 0.5-1.0 mg/kg/day is recommended for acne vulgaris [1]. However, in cases where side effects are not tolerated at the recommended dose, or when used in mild acne with significant psychological distress low

dose and/or intermittent treatment have been advocated in medical literature [**2, 3, 4**].

A clinical audit was carried out in a tertiary care hospital to determine current practice regarding oral isotretinoin use in acne vulgaris; whether oral retinoids are being admini stered according to clinical guidelines recommended by British Association of Dermatol ogists in 2010 [**5**] and to evaluate the association between adherence to guidelines and safety and efficacy profile.

Material and Methods

The clinical audit was conducted in a single tertiary care hospital, Aberdeen Royal Infirmary, Scotland. The data was obtained from the medical record of 400 patients of acne vulgaris who received oral isotretinoin from the period 2010 - 2013. Ethics approval was not sought, since identifiable data were not requested from participants, as per the policy of the hospital. Data was collected on demographic details like age, gender, weight, duration of acne, method of calculation of severity of acne, history of depression and the scoring system used to assess it, previous treatments used for acne, total duration and dose of isotretinoin, monitoring of laboratory investigat ions before, during and at the end of treatment, response of the disease and side effect profile. Results were collated and analyzed on SPSS 17 statistical software.

Results

Total of 400 patients' data was obtained. 51.8% (207 patients) were female and 48.3% (193patients) were male, with mean age 22.3 +7.2 years. The youngest patient was 13-year-old while the oldest was of 53 years. The average weight of the p atients was 68.33 +- 13.08 kg with a minimum weight of 42 kg and maximum of 135 kg. The general mood and inquiry about depression was documented in each patients' medical record prior to initiating therapy and on subsequent visits. However, the objective assessment of depression by Harvard National Depression Screening Day Scale (HANDS) [**6**] scoring system was done in 269 (67.3%) patients before initiation of treatment and by the third visit only 162 patients (60.2% of the original 269 on whom HANDS was administered) were assessed with it. 24 patients (6%) gave past history of depression and 11(2.75%) patients were suffering from depression and were on antidepressants at the time of initiation of oral isotretinoin.

Patients' acne was graded into four types; mild, moderate, severe and very severe, based on global facial acne severity scale [**7**] in all patients. The objective scoring by Global Acne Grading System (GAGS) [**8**] was done in 230 (57.5%) patients. Taking into consideration all 400 patients, 31 (7.8%) had mild acne, 237 (59.3%) had moderate, 129 (32.2%) had severe and 3 (0.8%) had very severe acne. All the patients had been treated with topical therapies and oral antibiotics in the past; 72 (18%), nearly one fifth, had taken oral isotretinoin course in the past.

Laboratory investigations like complete blood count, serum liver function tests and serum lipid profile were done at the beginning of treatment and then after every two months. The female patients were counseled to prevent pregnancy during treatment and for a month after stopping the drug. Before the commencement of therapy, urine for pregnancy test and serum beta HCG levels were done and repeated monthly during treatment and finally a month after stopping treatment.

Out of the total 400 patients forty (10%) were lost to follow up and eleven (2.75%) of the patients discontinued treatment due to side effects. Thus, a total of 349 patients completed acne course. There was a variation in the dose of isotretinoin recei ved by the patients. Mean dose was 117.31 +- 28.64, minimum dose of 48 and maximum was 263.64/kg body weight. Different cumulative doses of isotretinoin were used by the dermatologists for different grades of acne. To analyze the data, while computing the results four groups were created depending on the cumulative oral isotretinoin dose: Group I comprised of patients who received <80mg/kg of the drug, Group II of patients who received 80 – 119 mg/kg of the drug, Group III of patients who received 120 – 149 mg/kg and

Table 1. Different Groups of Patients Based on Cumulative Dose of Isotretinoin in mg/kg body weight (n=349)

Group	Dose (mg/kg body weight)	No of patients	Percent	Cumulative percent
I	< 80	27	7.7	7.7
II	80 - 119	158	45.3	53.0
III	120 - 149	127	36.4	89.4
IV	>149	37	10.6	100

Group IV of patients who received >150 mg/kg of the drug, shown in (**Table 1**). Majority of the patients (81.7%) fell in groups II and III. Patients took isotretinoin treatment for a mean duration of 6.7 +_ 1.5 months. Mean duration for groups I, II, III and IV were 4.9, 6.3, 7.2 and 7.6 respectively. Clinical response was graded as excellent, partial or poor. Clinical improvement was measured as excellent (when there was either complete clearance or almost complete clearance with less than five acne lesions at the time of stopping treatment), partial (mild acne at the time of stopping treatment) and poor (moderate to severe acne at the time of stopping treatment). Taking into account all 400 patients 347 (86%) of the patients had an excellent response with complete or near complete clearance of acne; 2 patients (0.5%) had a partial response with mild acne persisting at the time of discontinuation of therapy. 40 patients (10%) were lost to follow up and eleven (2.75%) discontinued treatment due to persistent side effects. The side effect profile is shown in (**Table 2**). The patients who had to discontinue the drug due to side effects are shown in (**Table 3**). Two female patients while on treatment became pregnant and both opted for therapeutic abortion.

There were 11 patients of depression at the start of the treatment. Five patients (45.45%) either had no effect on depression or their depression got better once the acne started improving. In three patients (27.3%) the symptoms worsened and their medication dose was increased and in one patient treatment had to be discontinued. Three patients (27.7%) were lost to follow up. Six patients became depressed while on treatment and had to take antidepressants. Half of them opted to discontinue isotretinoin because of worsening depression. As many as 36 (9%) of the patients reported some mood change/ not feeling their usual self.

Discussion

Oral isotretinoin is widely used for acne vulgaris since the early 1980s and since then it has shown to be extremely effective for severe and persistent acne. In fact, the drug is unrivalled in clinical efficacy and remission cap ability for acne treatment [**9**]. The drug administration requires appropriate monitoring and continued vigilance for safety concerns. We have examined the study results in the light of isotretinoin guidelines prepared by British Association of Dermatologists [**5**]. Conforming to the guidelines; isotretinoin is being prescribed by Consultant led team

Table 2. Percentage of Patients Exhibiting Different Side Effects of Oral Isotretinoin (n=400)

Side effect	No of patients	Percentage
None	14	1.4
Dryness of skin	382	95.5
Dryness of lips	380	95
Depression	6	1.5
Headache	21	5.3
Musculoskeletal symptoms	69	17.3
Nose bleeds	46	11.5
Mood changes	36	9.0
Abnormal lipid profile	9	2.3
Abnormal liver profile	5	1.3
Photosensitivity	7	1.8
Nausea, vomiting	1	0.3
Insomnia	2	0.5
Flushing	1	0.3
Uveitis	1	0.3
Alopecia	2	0.5
Irregular menstruation	1	0.3
Weight gain	1	0.3

Table 3. Table Indicating the Reason to Discontinue Isotretinoin (n=11)

Side effect	No of patients discontinuing treatment
Depression/ low mood	4
Musculoskeletal symptoms	4*
Nose bleeding	2*
Uveitis, photosensitivity	1
Dryness, bleeding from lips	1

only, comprising the following: consultants, dermatology trainees, non-consultant career grades, accredited GPs with special interest and dermatology specialist nurses.

Isotretinoin is being prescribed in different doses. It has been advocated that low dose regimens are better tolerated and effective in inducing acne clearance. Many of the adverse effects are dose dependent and appropriate low dosing may mitigate them [**2, 3, 4**]. The down side of low dosing is the possibility that lesser exposures have demonstrated a higher risk of earlier recurrence of acne vulgaris [**10**]. It has been suggested that although a threshold dose of 120 – 150 mg/kg is widely regarded as increasing remission potential the optimal cumulative doses required to induce remission appears to vary with severity [**11**]. Blasiak et al [**12**]. exposed their patients to significantly higher cumulative doses. They found that patients receiving 220 mg/kg or more had a significantly decreased risk of relapse, with no significant increase in adverse effects. This audit also reflects that the ideal dosing regimen is unknown. A variation in prescribing cumulative doses was seen. This may also be due to the fact that the drug has been used for treating mild to moderate acne associated with psychological morbidity.

It is well documented that isotretinoin is a potent teratogen and female patients should avoid pregnancy during and for at least one month after the end of the treatment [**13**]. Isotretinoin exposure during pregnancy can lead to a range of severe craniofacial, cardiac, CNS abnormalities and increased rates of spontaneous abortion. Despite the well documented teratogenic hazard many studies have shown poor adherence to pregnancy prevention guidelines [**14, 15, 16**]. During our study period 2 of total 193 (1.04%) patients became pregnant. The hospital follows the Pregnancy Prevention Programme (PPP) that has been adopted by the Medicines and Healthcare Products Regulatory Agency (MHRA). The medical notes r ecord the menstrual and sexual history/behavior. Practically every woman had received information of the methods of contraception, about the risks of teratogenicity with isotretinoin and they had signed the form to confirm that they had received information of the teratogenic risk of the drug and methods of contraception. Females did not get extended periods of treatment without having pregnancy tests performed. They were given a 30 day supply on each visit after medically supervised pregnancy testing.

It is well known that the drug crosses the blood brain barrier; can cause benign intracranial hypertension and headache. This lays down the theoretical basis for mood alteration [**17**]. Among the possible side effects of isotretinoin, depression, suicidal ideation and suicide are important aspects not to be ignored [**18**]. The iPLEDGE consenting warns about the risk of depression and suicidal ideation, there is no recommendation for screening tools [**19**]. The BAD guidelines [**5**]. have suggested more extensive screening using a validated questionnaire like the Beck questionnaire [**20**]. the HANDS questionnaire [**6**]. or the six-question screening tool [**21**]. In this audit period all the medical notes showed that the patients were questioned about mood and present and/or past history of depression. However, HANDS scoring was done in 67% only. It is recommended that a scoring system or any uniform question screening tool should be employed to efficiently screen for depression before and during isotretinoin use. The complex relationship between acne and depression was seen during the audit as has been noted before in medical literatur e. Although heavily implicated with mood

change and depression there are studies that suggest that as oral isotretinoin clears the acne it causes significant reduction in depression scores [**22**]. Others have refuted that the evidence linked with depression and suicidal ideation is weak [**23**].

The proportion of patients with laboratory abnormalities in liver function and lipid profile was low. This result is similar to the systematic review and meta-analysis done by Lee et al [**24**]. which concluded that the evidence does not support monthly laboratory testing for use of standard doses of oral isotretinoin for the standard patient with acne. Simultaneously, there is data suggesting that the development of hyperlipidemia during treatment may be a marker for the development of significant hyperlipidemia in later life [**25**].

Conclusion

This audit contributes that there is abstruseness regarding optimization to maximize response while minimizing the potential for avoidable adverse events. Patients with mild to moderate acne may achieve complete healing of the lesions with doses much less than the classical recommended ones. This may incur lesser burden of cost as well as less chances of side effects. Oral isotretinoin is a well-tolerated drug and only a small percentage of patients had to discontinue medicine due to its side effects. The relationship between isotretinoin treatment for acne and depression is complex with cases depression getting better as their acne improved and some having to stop medicine because of worsening acne. The audit indicates that standardized approach/authentic tool to measure depression in patients are imperative. The tool should be simple and effective to be implemented easily in the OPD. Despite rigorous measures to avoid pregnancy in women of child bearing age, two female patients got pregnant indicating more needs to be done. Dermatologists need to adhere to the current guidelines as oral isotretinoin is an effective and well-tolerated drug when used under supervision.

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