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# Treatment of Severe Acne with Low-dose Isotretinoin

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Acne vulgaris is the most common skin disorder with possibly significant social consequences for those affected. Acne conglobata is a severe, inflammatory, nodulocystic form of acne (1), and acne fulminans is a severe, ulcerative form of acne with an acute onset and systemic symptoms (2). Acne has a complex pathogenesis with likely factors including increased seborrhoea, ductal cornification, and colonization of the pilosebaceous ducts by *Propionibacterium acnes* with ensuing inflammation, as well as elevated insulin-like growth factor 1 (IGF-1 levels (3) and increased signalling via the fibroblast growth factor receptor 2 pathway (4). Inflammation seems to result ultimately from an increased production of interleukin 1 beta and tumour necrosis factor-α (5). A wide array of treatment options, including systemic isotretinoin are available (6).

The aim of this study was to show that a low-dose isotretinoin therapy, 0.1–0.3 mg/kg daily, can be effective in treating severe forms of acne.

## METHODS

A retrospective analysis of 4 patients with acne conglobata or acne fulminans treated with low-dose isotretinoin (0.1–0.3 mg/kg/day) was performed. The primary endpoint was the photodocumented improvement of the skin lesions during therapy, quantified using Cook's grading scale for acne (7), a method grading the severity of skin lesions on a scale from 0 (≤ 3 comedones/papules) to 8 (most severe, i.e. highly inflammatory acne, acne conglobata) using photographic standards. Secondary endpoints were the occurrence of side-effects, therapy duration and cumulative isotretinoin dose. The use of topical therapeutics or other medication for acne treatment was reviewed. Before starting treatment, pregnancy of female patients was ruled out. Patients had been informed of the strict necessity to use reliable methods of contraception until one month after treatment cessation. Patients underwent routine laboratory checks including a full blood count, liver function tests, and a serum lipid profile before treatment initiation and during treatment, as well as routine clinical examination for the monitoring of side-effects.

## RESULTS

The study sample comprised 4 patients; all were between 14 and 18 years of age at the start of treatment (Table I). All patients initially had a Cook's grading scale acne score of 8 and received isotretinoin 10–20 mg daily; 3 were also treated intermittently with oral corticosteroids for 7–9 weeks. The patients were treated for a mean of 10.4 months, with a mean daily isotretinoin dose of 0.19 mg/kg, and a mean cumulative dose of 65.8 mg/kg. Three of 4 patients also recieved topical treatment (adapalene, clindamycin in combination with benzoyl peroxide or erythromycin). After treatment, one patient had a Cook's grading scale acne score of 0, two of 2 and one patient of 4 (Fig. 1). The side-effects were mild. Except for one patient with persistently elevated serum cholesterol and creatine kinase, the laboratory findings normalized during treatment without further intervention.

## DISCUSSION

Isotretinoin is indicated for severe nodular acne that is unresponsive to combined oral therapy with antibiotics and topical therapy, or under special clinical circumstances as a first-line therapy in individual cases, at a dose of 0.5–1.0 mg/kg/day, with a cumulative dosage of 120–150 mg/kg over 4–6 months (8). Adverse effects include dry skin and mucosa (9), elevated liver enzymes

Table I. *Therapeutic effects of low-dose isotretinoin in 4 cases of severe acne*

| Pat. no/ Sex | Diagnosis | Clinical response[a] | Mean dose (mg/kg/day) | Cumulative dose (mg/kg) | Duration (months) | Adjuvant medication | Topical therapy | Side-effects |
|---|---|---|---|---|---|---|---|---|
| 1/M | Acne conglobata | 8 to 0 | 0.25 | 60.5 | 8.1 | None | None | Elevated serum cholesterol, creatinine kinase at last visit, mild cheilitis |
| 2/M | Acne fulminans | 8 to 2 | 0.18 | 55.5 | 10.0 | Oral methyl-prednisolone | Adapalene gel | Transient elevation of serum TG, mild cheilitis |
| 3/F | Acne fulminans | 8 to 4 | 0.15 | 34.8 | 7.4 | Oral predni-solone | Clindamycin/ benzoyl-peroxide | Transient elevation of serum cholesterol, γ-GT, TG, mild cheilitis |
| 4/M | Acne conglobata | 8 to 2 | 0.16 | 112.3 | 16.2 | Oral predni-solone | Erythromycin cream | Transient elevation of cholesterol, TG, alkaline phosphatase, mild cheilitis |

[a]Cook's grading scale.
TG: triglycerides; γ-GT: γ-glutamyltransferase.

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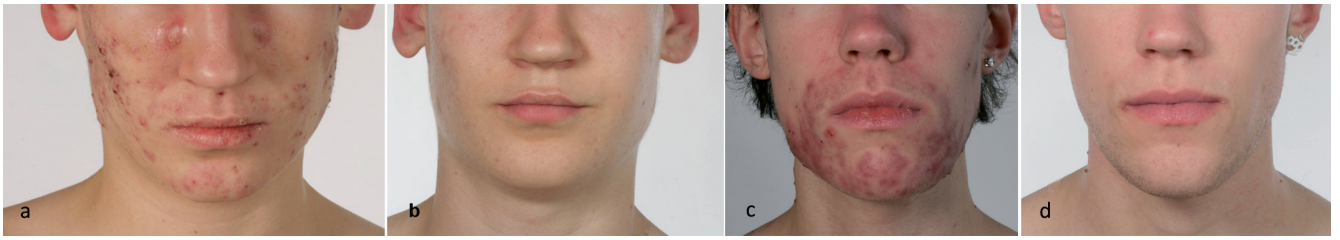


*Fig. 1.* Patient 2. (a) Before treatment, Cook's grading scale acne score of 8. (b) After treatment, 0.18 mg/kg/day for 10.0 months, score 2. Patient 4. (c) Before treatment, score of 8. (d) After treatment, 0.16 mg/kg/day for 16.2 months, score 2.

and an increase in serum lipids, especially triglycerides (10), most of the side-effects being dose-dependent. Isotretinoin is highly teratogenic, with a reported 40% incidence of birth defects occurring in children who have been exposed to isotretinoin during the first trimester of pregnancy (9). Most of the side effects, such as dryness of the lips and skin, are dose-dependent, although this can not be asserted for isotretinoin's teratogenicity (12, 14). Moreover, isotretinoin of less than 0.2 mg/kg is reported to reduce the risk of acne flare upon initiation of therapy (11). This study clearly shows that severe forms of acne can be treated effectively with low-dose isotretinoin (0.1–0.3 mg/kg), if necessary in combination with oral prednisolone, all 4 treated patients improving significantly. Our results are supported by the findings of Plewig et al. (12) and of Lee et al. (13), who demonstrated the effectiveness of low-dose isotretinoin in the treatment of acne conglobata and moderate acne, respectively. Karvonen et al. (14) demonstrated the effectiveness of combining long-term isotretinoin therapy with an initial course of systemic prednisolone in cases of cystic acne. Strong indirect evidence supports the mechanism of action of isotretinoin through the upregulation of FoxO transcription factors, thus dampening promotive effects in the pathogenesis of acne (15). Our patients did not experience a flare of acne upon treatment initiation, nor did any patients show signs of neuropsychiatric problems. None complained about dry eyes or skin, although all developed a mild cheilitis. The laboratory findings were mild and in all but one case resolved spontaneously. None of the patients had to stop isotretinoin therapy due to side-effects. In conclusion, the efficacy and favourable side-effect profile strongly support the use of low-dose isotretinoin treatment, 10–20 mg/day, as first-line therapy for acne conglobata, and in combination with a short-term course of oral corticosteroids, also for acne fulminans. Larger studies are necessary to validate our findings. Moreover, it will be interesting to determine the rate of recurrence of severe forms of acne treated with low-dose isotretinoin.

*The authors declare no conflicts of interest.*

## REFERENCES

1. Plewig G, Kligman AM. Acne and rosacea. 3rd edition. Berlin: Springer Verlag, 2000.
2. Zaba R, Schwartz R, Jarmuda S, Czarnecka-Operacz M, Silny W. Acne fulminans: explosive systemic form of acne. J Eur Acad Dermatol Venereol 2011; 25: 501–507.
3. Kurokawa I, Danby FW, Ju Q, Wang X, Xiang LF, Xia L, et al. New developments in our understanding of acne pathogenesis and treatment. Exp Dermatol 2009; 18: 821–832.
4. Melnik BC, Schmitz G, Zouboulis CC. Anti-acne agents attenuate FGFR2 signal transduction in acne. J Invest Dermatol 2009; 129: 1868–1877.
5. Kang S, Cho S, Chung JH, Hammerberg C, Fisher GJ, Voorhees JJ. Inflammation and extracellular matrix degradation mediated by activated transcription factors nuclear factor-kappaB and activator protein-1 in inflammatory acne lesions in vivo. Am J Pathol 2005; 166: 1691–1699.
6. Strauss JS, Krowchuk DP, Leyden JJ, Lucky AW, Shalita AR, Siegfried EC, et al. Guidelines of care for acne vulgaris management. JAAD 2007; 56: 651–663.
7. Cook CH, Centner RL, Michaels SE. An acne grading method using photographic standards. Arch Dermatol 1979; 115: 571–575.
8. James WD. Clinical practice. Acne. N Engl J Med 2005; 352: 1463–1472.
9. Goodfield MJD, Cox NH, Bowser A, McMillan JC, Millard LG, Simpson NB, et al. Advice on the safe introduction and continued use of isotretinoin in acne in the UK 2010. Br J Dermatol 2010; 162: 1172–1179.
10. Barth JH, Macdonald-Hull SP, Mark J, Jones RG, Cunliffe WJ. Isotretinoin therapy for acne vulgaris: a re-evaluation of the need for measurements of plasma lipids and liver function tests. Br J Dermatol 1993; 129: 704–707.
11. Borghi A, Mantovani L, Minghetti S, Virgili A, Bettoli V. Acute acne flare following isotretinoin administration: potential protective role of low starting dose. Dermatology 2009; 218: 178–180.
12. Plewig G, Dressel H, Pfleger M, Michelsen S, Kligman AM. Low dose isotretinoin combined with tretinoin is effective to correct abnormalities of acne. J Dtsch Dermatol Ges 2004; 2: 31–45.
13. Lee JW, Yoo KH, Park KY, Han TY, Li K, Seo SJ, et al. Effectiveness of conventional, low-dose and intermittent oral isotretinoin in the treatment of acne: a randomized, controlled comparative study. Br J Dermatol 2011; 164: 1369–1375.
14. Karvonen SL, Vaalasti A, Kautiainen H, Reunala T. Systemic corticosteroid and isotretinoin treatment in cystic acne. Acta Derm Venereol 1993; 73: 452–455.
15. Melnik BC. Isotretinoin and FoxO1: a scientific hypothesis. Dermatoendocrinol 2011; 3: 141–165.