Isotretinoin
A Review of its Pharmacological Properties and Therapeutic Efficacy in Acne and Other Skin Disorders

A. Ward, R.N. Brogden, R.C. Heel, T.M. Speight and G.S. Avery

ADIS Drug Information Services, Auckland

Various sections of the manuscript reviewed by: R. Becke, Gordon, New South Wales, Australia; B. Berretti, Department of Dermatology, Polyclinique d'Aubervilliers, Aubervilliers, France; M. Binazzi, Instituto di Clinica Dermatologica e Venereologica dell'Università di Perugia, Policlino Monteluce, Perugia, Italy; P.M. Elias, Department of Dermatology, Veterans Administration Medical Center, San Francisco, California, USA; E.C. Gomez, Department of Dermatology, University of California, Davis, California, USA; A.M. Kligman, Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania, USA; J.M. Marks, Department of Dermatology, Royal Victoria Infirmary, Newcastle upon Tyne, England; R. Marks, Department of Medicine, Welsh National School of Medicine, Cardiff, Wales; R.G. Park, Wellington, New Zealand; G.L. Peck, Department of Health, Education, and Welfare, Bethesda, Maryland, USA; G. Plewig, Universitäts Hautklinik, Düsseldorf, West Germany; I. Racz, Clinic of Dermatology, Semmelweis Medical School, Budapest, Hungary; H.H. Roenigk, Department of Dermatology, Northwestern University, Chicago, Illinois, USA; J.S. Strauss, Department of Dermatology, University of Iowa, Iowa City, Iowa, USA; D.S. Wilkinson, The Chiltern Hospital, Great Missenden, Buckinghamshire, England.

Contents

Summary .................................................................................................................. 7
1. Pharmacodynamic Studies .............................................................................. 9
   1.1 Effects on the Sebaceous Gland ................................................................. 9
      1.1.1 Animal Models .................................................................................. 9
      1.1.2 Human Studies ............................................................................... 9
   1.2 Effects on Tumour and Epidermal Cell Proliferation and Differentiation .... 11
   1.3 Immunological and Anti-Inflammatory Effects ......................................... 12
   1.4 Effects on Skin Microflora ........................................................................ 13
2. Pharmacokinetic Studies ................................................................................ 14
   2.1 Absorption .............................................................................................. 14
   2.2 Distribution ............................................................................................. 14
   2.3 Metabolism and Excretion ....................................................................... 14
      2.3.1 Half-Life ......................................................................................... 16
3. Toxicology ....................................................................................................... 17
   3.1 Acute Toxicity ......................................................................................... 17
   3.2 Subacute and Chronic Toxicity .................................................................. 18
3.3 Teratogenicity and Reproduction Studies ........................................... 18
3.4 Carcinogenicity, Mutagenicity and Chromosomal Studies ................. 19
4. Therapeutic Trials ............................................................................. 19
4.1 Acne ......................................................................................... 19
4.1.1 Open Studies ....................................................................... 19
4.1.2 Controlled Studies ............................................................... 22
4.1.3 Post-Treatment Follow-up Studies ......................................... 22
4.1.4 Factors Affecting Response to Therapy .................................... 24
4.2 Rosacea and Gram-Negative Folliculitis ....................................... 24
4.3 Miscellaneous Disorders of Keratinisation ..................................... 24
4.3.1 Psoriasis ............................................................................. 24
4.3.2 Darier's Disease ................................................................. 24
4.3.3 Ichthyosis .......................................................................... 25
4.3.4 Pityriasis Rubra Pilaris ......................................................... 25
4.3.5 Other Disorders ................................................................... 27
4.4 Premalignant and Malignant Diseases ........................................... 27
5. Side Effects ................................................................................... 28
5.1 Effects on Serum Lipid Levels and Other Laboratory Parameters .... 30
6. Dosage and Administration .......................................................... 30
7. Place of Isotretinoin in Therapy ....................................................... 32

Synopsis: Isotretinoin\(^1\) is a new orally active retinoic acid derivative for the treatment of severe refractory nodulocystic acne. The pharmacological profile of isotretinoin suggests that it acts primarily by reducing sebaceous gland size and sebum production, and as a result alters skin surface lipid composition. Bacterial skin microflora is reduced, probably as a result of altered sebaceous factors. Isotretinoin 1 to 2 mg/kg/day for 3 to 4 months produces 60 to 95% clearance of inflammatory lesions in patients with severe, recalcitrant nodulocystic acne, with evidence of continued healing and prolonged remissions in many patients after treatment withdrawal. Doses as low as 0.1 mg/kg/day have also proven successful in the clearance of lesions; however, with such low doses the duration of remission after treatment withdrawal is usually shorter. Encouraging results have also been seen in small numbers of patients with rosacea, Gram-negative folliculitis, Darier's disease, ichthyosis and pityriasis rubra pilaris, the response in keratinising disorders resembling that with the related drug etretinate. While long term follow-up studies in these patients have not been reported, prolonged remission after withdrawal of isotretinoin in disorders of keratinisation is unlikely, as with other drugs used in these conditions. Isotretinoin is only partially effective in psoriasis, in contrast to etretinate which is very effective in psoriasis but ineffective in severe acne. Some encouraging results have also been reported with isotretinoin in patients with squamous and basal cell carcinomas, but isotretinoin has proven unsuccessful in non-squamous cell epithelial and non-epithelial cancer. Side effects affecting the mucocutaneous system occur in nearly all patients receiving isotretinoin, but rarely lead to drug withdrawal. Raised serum triglyceride levels are also commonly reported. The possibility of long term spinal or skeletal bone toxicity may restrict the use of isotretinoin in severe disorders of keratinisation requiring prolonged administration. Isotretinoin is strictly contraindicated in women of childbearing potential due to its severe teratogenic properties, unless an effective form of contraception is used.

Thus, isotretinoin offers an effective advance on the treatment options available in a difficult therapeutic area – those patients with severe, nodulocystic acne not responding to ‘traditional’ therapy.

\(^1\) ‘Accutane’ (Roche).