Isotretinoin: an enormous landmark in the treatment of severe acne

In our latest article on landmark drugs, Jenny Bryan looks at how isotretinoin transformed the lives of thousands of teenagers with acne.

Like it or loathe it, the acne treatment isotretinoin has transformed the lives of thousands of teenagers since it was licensed in the UK in 1983. At a time when dermatologists resorted to leprosy drugs and systemic steroids to treat the most severe cases of acne, the arrival of isotretinoin was widely welcomed despite its teratogenic properties which were recognised from the start.

“It was an enormous landmark in acne treatment and provided dermatologists with something that could bring acne under control in 98 per cent of patients. When isotretinoin first came out, there was an enormous sigh of relief that, at last, we had something that worked, and we were glad to be able to offer a potential cure to our patients,” recalls Anthony Chu, professor of dermatology, Buckingham University, consultant dermatologist, and honorary senior lecturer, Imperial College, London.

Increasingly stringent systems were introduced to reduce the number of women who became pregnant during isotretinoin treatment. But it was not until 1998, when over eight million patients had been treated with the drug, that warnings were added to the drug’s UK datasheet that isotretinoin could cause depression, psychotic symptoms and, rarely, suicide attempts and suicide.

“When the issue first came up, people weren’t surprised that patients were depressed and assumed it was due to their acne. But then we started to see previously happy people who suddenly became depressed, went away, and committed suicide, and that was a big shock,” says Professor Chu.

High efficacy rates but relapses, too

Originally investigated as a cancer treatment — and currently on trial in advanced brain and other tumours — 13-cis retinoic acid (isotretinoin) is a synthetic isomer of naturally occurring transretinoic acid, a metabolite of vitamin A. It was developed and marketed by Hoffmann-La Roche, though declining market share in the face of generic competition and the cost of defending personal injury litigation led Roche to discontinue manufacture and distribution in the US in June 2009. The company still markets the drug in the UK, and a spokesman was unaware of any plans to withdraw it.

Isotretinoin reduces the size of the sebaceous glands and sebum production, with accompanying normalisation of keratinocyte growth and prevention of follicular hypercornification — one of the primary changes in acne. This leads to reduced inflammation, death of bacteria and healing of lesions.

The outstanding effects of isotretinoin on acne were first reported in a small open study of 14 patients with treatment-resistant cystic acne.13 Of the patients had complete remission of their acne and the other had 75 per cent improvement. At the time of publication, the researchers reported remission lasting up to 20 months after discontinuation of treatment. Skin and mucous membrane side effects were recorded as dose-dependent and reversible when treatment was stopped.

Subsequent studies showed that 90 per cent of patients achieved a 70 per cent improvement in acne severity when treated with isotretinoin 0.1mg/kg/day to 1mg/kg/day for 12 to 24 weeks, and a starting dose of 0.5mg/kg/day was recommended.1 A dose of 0.5–1 mg/kg/day is currently advised, with a typical total dose of 120mg/kg over a four-month treatment period. However, about 50 per cent of patients relapse on standard doses and, as Professor Chu explains, it is impossible to predict who those patients will be.

“You cannot look at patients and say who will respond according to their skin type or severity of their acne, nor can you predict who will get what can be devastating side effects,” he says.
Professor Chu points out that poor responders or early relapers to a first course of isotretinoin treatment will not respond better to further courses, and should be discouraged from trying again. Indeed, he is wary of re-treating even good responders months or years after a first course because serious side effects can still occur in patients who tolerated the drug well during a first course of treatment.

Side effects can be devastating
The mild, reversible side effects reported in the first isotretinoin trials have not proved as mild or reversible in some patients as originally expected. At least one in 10 people get inflammation and cracking of the lips, dermatitis, dry or scaly skin, itching, rash and/or fragile skin. For some, the lip cracking can be so severe that they can only drink through straws, and the dry and itchy skin can be uncomfortable and distressing. Rarely, these side effects can persist for years after the drug has been stopped. A small proportion of people (≤1 in 10,000) get acne fulminans — sudden, severe, painful ulcerated acne anywhere on the body, which may be accompanied by fever and joint pain. This can be difficult to control and may leave patients with extensive scarring.

The risk and severity of psychiatric side effects of isotretinoin is the subject of heated debate on the internet. The Medicines and Healthcare products Regulatory Agency guidance puts the risk of depression, aggravation of existing depression, aggressive tendencies, anxiety and changes in mood at ≥1 in 10,000 but <1 in 1,000 patients. For abnormal behaviour, psychotic disorder, suicidal ideation, attempted suicide and suicide, it puts the risk at 1 in 10,000 patients or fewer.

Overuse puts patients at risk
Professor Chu is concerned that, despite well publicised side effect problems, isotretinoin is overused. In the UK, prescriptions can only be initiated by a consultant dermatologist, and women of childbearing potential must agree to use at least one or preferably two methods of contraception and take regular pregnancy tests. But isotretinoin can be bought easily on the internet where it is sold with some of the users, rather than with the manufacturer. It’s a double-edged sword, and the problem is undoubtedly a great drug when it’s used correctly. But it’s a double-edged sword, and the problem is with some of the users, rather than with the drug.”

References
1. Rother discontinue plans to delist accutane in the US. Available at www.gene.com (accessed 12 November 2009).

Where else would you study such professionally orientated courses?
Located in the heart of the city, the School of Social Sciences at City University London is the ideal place to expand your mind.

The School of Social Sciences at City University London is a vibrant place of teaching, learning and research. With an exceptional reputation for graduate employability a postgraduate degree from City University provides an excellent step up to your future career. We combine first-class teaching with an exciting programme of postgraduate courses and offer a number of specialist degree programmes including:
* MSc Economic Evaluation in Healthcare
* MSc in Health Economics
* MSc in Social Research Methods (5 pathways including Psychology, Statistics and Sociology)

Put your mind to work...
For further information or to receive an application pack please contact our postgraduate enquiries service on +44 (0)20 7040 8512 or email socscipg@city.ac.uk and quote reference PJ1109

www.city.ac.uk/social