Roaccutan® (Isotretinoin) Roche off Registration in Denmark since April 9th 2007

Some facts, and some personal thoughts, on scaring, scarring and under-treatment of acne

Jørgen Serup, MD, Chief Editor
Bispebjerg Hospital, Department of Dermatology, Copenhagen, Denmark
Linköping University, Department of Dermatology, Linköping, Sweden

A few weeks ago, Danish dermatologists received a letter from Marketing Director Hanne Schultz Kapel, Roche a/s, Denmark; stating that Roche, the original developer of the revolutionary acne medication Roaccutan®, has decided to take it off the Danish market. Registration and sales will be maintained in the other Nordic countries. The reason behind this decision is the Danish regulations, which grant massive benefits to the six generic isotretinoins on sales in Denmark. The free market is not free, since only the very cheapest one at any time will receive reimbursement. In practice, however, only Roche a/s can and will support dermatologists with literature and informations from their huge database of records that has accumulated over many years. With no medication on the Danish market, naturally access to this wealt of information will be stopped.

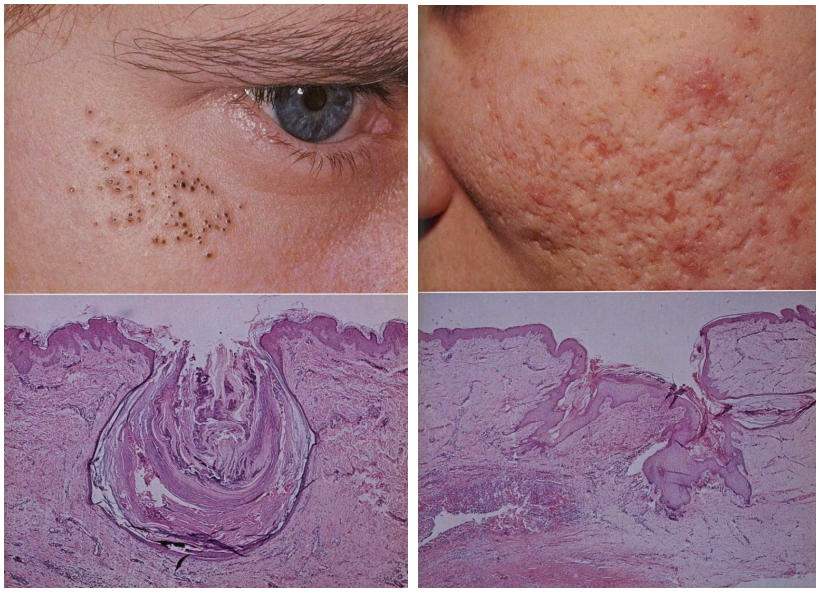
Having witnessed the days before isotretinoin; when many acne patients using old remedies had their faces disfigured by scarring and became miserable during their difficult teen years; and having vitnessed the therapeutic revolution created by Roaccutan®; I feel it is sad as well as unfair that the original developer; F. Hoffmann-La Roche Ltd.; is withdrawing this drug from the Danish market. The development of Roaccutan® must have been remarkably difficult, as well as expensive and risky due to the teratogenic effect, but F. Hoffmann-La Roche Ltd. mastered their educational obligation to the dermatological community and the patients, and fulfilled from the very start the special need of strict pharmaco-vigilance raised by the high risk of malformations. The company directors, who made the decision to go ahead with this huge effort, were courageous. No public institution, no pharmacy, no dermatologists and of course no generic company or parallel drug importer could ever have done the job. Roaccutan® is a historical drug in dermatology and will remain an indisputed breakthrough in modern acne therapy.

In Norway, Roaccutan® is on restricted prescription since its launch, and has no general marketing license and, thus, for technical reasons beyond copying in this country albeit new EC regulation may change this. Roaccutan® of Roche so far remains available in the other Nordic countries. Limitations of prescription in different versions in different countries were of course implemented since the launch back in the early eighties, due to the known risk of malformations.

In 1998 the media launched the idea of isotretinoin causing psychiatric morbidity and suicide, based on one tragic case in the USA. There was no evidence-based verification of a causal relationship. The media, especially television and magazines, nevertheless made it a public boom, which in Europe peaked around 2000. Patients and doctors were scared and reacted immediately; the drug agencies introduced tight limitations and sales of isotretinoin products dropped to about half of the normal level, as illustrated from data of the Swedish Drug Agency (unit DDD, 1 DDD = 30 mg isotretinoin)

Year 2000	2.391.360
Year 2001	2.083.211
Year 2002	1.736.095
Year 2003	1.353.777
Year 2004	1.458.540
Year 2005	1.427.077
Year 2006	1.284.754

Figures from the Danish drug agency have been requested and are under development.



From inflammation and comedone to scar, acne untreated.

Today, in 2007, a number of reviews based on large materials have been published, and a statistical and causal relationship between isotretinoin and psychiatric morbidity and suicide among acne patients has not been found (1, 2). These reviews are conducted according to the best standards of academic medicine. Of course an exceptional or "idiosyncrasic"case of adverse event can never be ruled out; as it cannot be ruled out for any other systemic medication including all medications we normally consider to be quite innocent. Logically and academically, with these reviews in hand, the use of isotretinoin should be back to the previous levels, but it remains half of what it was in 2000, as illustrated by Swedish figures (figures from before 2000 not available as per April 2007). Isotretinoin was in the early nineties a mature drug: well assessed and positioned in therapeutic practice. Consequently, many acne patients appear under-treated today, and we should probably, in 2007, double the number of active treatments.

As mentioned, the drug agencies imposed strict limitation of prescriptions and special surveillance of isotretinoins around 2000, but thereafter they have been silent. One can ask simple questions: are the agencies just collecting surveillance data year by year just to be kept on file, or are the data actively evaluated now and then and the risk assessment updated? Unnecessary restrictions should of course be removed if they lack factual basis over time; and if the outcome of these restrictions is under-treatment of acne with facial scarring as a result, it is a high price to pay for the acne sufferers. The media will not cover this discussion, and clear up their own misconception back in 1998. It is the obligation of the medical profession and the agencies to update, reevaluate and draw conclusions.

The American Academy of Dermatology writes, in the April 2007 number of the Blue Journal (3) in their recent guideline of care for acne vulgaris management stated on isotretinoin, which is registered for severe recalcitrant nodular acne: It is the unanimous opinion of the acne workgroup that oral isotretinoin is also useful for the management of lesser degrees of acne that are treatment-resistent or for the management of acne that is producing either physical or psychological scarring. And the guideline continues: Mood disorders, depression, suicidal ideation and suicides have been reported in patients taking this drug. However, a causal relationship has not been established. A recent clinical update in retinoid therapy of acne article from Europe came to a similar conclusion (4). Recent regulations on prescription, registration and use of isotretinoin by the FDA and by the EC with the primary aim to harmonize the text of summary of product characteristics, SPCs, have been met with skepticism by clinicians, who may see restrictions as ethically not acceptable since reduction and delay in treatment with isotretionin will increase scarring in some patients (5, 6).

Much can, of course, change if prescribing dermatologists themselves take the clear message that as per 2007 the fear of causal relationship between isotretinoin treatment and psychiatric morbidity in acne, despite much awareness, never found

statistical support, and consequently loosen their prescription routine to what it was before the media alert in 1998. This practically means using isotretinoin more than it has been hitherto. Medical doctors should of course primarily base their treatment decisions on logics and rationales, as well as the needs and the views of individual patient, and not on media alerts. Scared dermatologists produce scarred acne patients!

Roaccutan® of Roche a/s disappeared in little Denmark in April 2007, under conditions which I do not feel to be just. This original drug could easily have lived much longer and done a great deal of good in future. It was strangulated by politics and bureaucracy. Dermatologists are left with a handful of copies that come and go, but no serious long-term company back up of the product. Roaccutan® made the most important breakthrough in acne treatment in the last century and raised the level of dermatological therapy. Isotretinoin for acne could, as mentioned, not have been developed by any university or public institution; but public regulation can kill a product; as has happened with Roaccutan® in Denmark. May Roaccutan® get the respect and use it deserves in Sweden, Norway, Finland and Iceland and around the world in future! Denmark is left with opportunistic copies of the original, sponsored by public regulation.

I invited Roche a/s, Hanne Schultz Kapel to comment on the withdrawal of Roaccutan® in Denmark in this number of Forum for Nordic Dermato-Venereology.

I had and have no conflict of interest in relation to Roche a/s. This article was prepared purely on my own initiative.

References

1. Magin P, Pond D, Smith W. Isotretinoin, depression and suicide: a review of evidence. Br J Gen Practice 2005; 55: 134–138.
2. Marueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. Semin Cutan Med Surg 2005; 24: 92–102.
3. Strauss JS, Krowchuk DP, Leyden JJ, Lucky AW, Shalita AR, Siegfried EC, Thiboutot D, Van Voorhees AS, Beutner KA, Sieck CK, Bhushan R. Guidelines of care for acne vulgaris management. J Am Acad Dermatol 2007; 56: 651–663.
4. Layton AM, Dreno B, Gollnick HPM, Zouboulis CC. A review of the European Directive for prescribing systemic isotretinoin for acne vulgaris. J Eur Acad Derm Venereol 2006; 20: 773–776.
5. Thielitz A, Krautheim A, Gollnick. Update in retinoid therapy of acne. Dermatol Therapy 2006; 19; 272–279.