

*O'CONNELL*

## Medical Officer's Review

APR 15 1998

NDA Briefing Psychiatric Adverse Events

NDA 18-662

(Volume 132.1/2)

Submission date: 29 Jan 98  
Review Completed: 02 March 98  
Sponsor: Roche Pharmaceuticals

Drug: Accutane® (13-cis-retinoic acid, isotretinoin, Ro 04-3780)

Pharmacologic Category: Retinoid

Indication: Severe recalcitrant nodular acne

Dosage Form/Route: Capsule/Oral

**Summary:** In May 1997 we discussed with the Sponsor our increasing concern regarding the seriousness of psychiatric adverse events being reported with Accutane use (see attached memorandum dated May 1997 which includes initial consult from Pharmacovigilance). Special emphasis was placed on the pattern of the events and the cases with positive de-challenge and/or re-challenge. At the time of the teleconference, most of the Sponsor participants did not agree that the reports reflected effects of Accutane; instead, they felt that the reports reflected underlying psychiatric disease in the population being treated. Nonetheless, the Sponsor agreed to investigate further and reply to our concerns in a timely manner. After 6 months, we again contacted the Sponsor, who reported that the data was still under review. Because of the seriousness of the events in question and the possibility of a true drug relationship based on our analysis, we proceeded to send the Sponsor a formal request for a labeling change and a Dear Doctor letter. This action was followed by several submissions from the Sponsor containing published literature and preliminary analyses of the same data we had examined (MedWatch), as well as identification of expert consultants for the Sponsor. The January 29, 1998 submission to be reviewed here was sent in preparation for a February 2, 1998 meeting of the Sponsor, three of their consultants, and the Agency (HFD-540, Dr. Weintraub, HFD-733, Dr. Goldman/MedWatch, DDMAC). The submission includes the following:

- 1) Curriculum vitae and highlights of the experts' findings (Judith Jones, MD/PhD-pharmacoepidemiology; Douglas Jacobs, MD-psychiatry; and David Bickers, MD-dermatology).
- 2) Source documentation supporting the experts' findings.

- 3) MedWatch reports up to November 1997.
- 4) Patient line listings: suicides, suicide attempts, depression, psychosis.
- 5) A compilation of wording for drugs currently labeled with psychiatric adverse events related to suicide.

#### Review of the epidemiologic data submitted

Dr. Jones addressed the questions of whether there is an emerging problem, whether the reports are related to Accutane, and whether there is a public health problem. The question of an emerging problem is not at issue because our request for action was not based on increasing incidence reports. Rather, it was based on the seriousness of accumulating reports and on the pattern of robust positive dechallenge and rechallenge cases. The value of positive dechallenge and rechallenge cases in establishing product-event associations is well-documented (Temple RJ, Jones JK, Crout JR *NEJM* 1979; 300:1046).

A comparison of "expected" events to "observed" events is informative if the number of "observed" events is higher than expected. The "observed" events are the number of reports to the manufacturer and/or MedWatch. Thus, conclusions based on a comparison of expected numbers of suicides/attempts to the observed number requires an assumption that the "observed" number, even if adjusted, approximates the actual number. Accutane has been on the market since 1982. It is well established that spontaneous adverse event reporting decreases over time after approval (see *The Clinical Impact of AE Reporting*, FDA/MedWatch, Oct 1996).

The submission by Dr. Jacobs (psychiatrist) stated that the overall rate of suicide in the US is unchanged since 1972. The Sponsor's December 8 submission stated that the rate of suicide for adolescents increased by more than 200% from 1982 to 1992, the date of publication of the referenced paper (Hodgman CH, McAnaney ER, *Hosp Pract* 1992; 127:73). This publication was presented to support the idea that the reports we are seeing reflect baseline psychiatric disease in the population likely to be using Accutane (people with acne). As noted above, Accutane was approved in 1982. The Sponsor also noted that in this period, over 28 million prescriptions for Accutane have been filled.

Regarding suicide attempts, the Sponsor states that since introduction of ROACCUTAN® in 1982 until November 24, 1997, 37 cases of attempted suicide were received by ROCHE Drug Safety. The 15 day serious adverse event reports I have received from Roche for 1996 and 1997 alone include 11 reports of suicide attempts (see appended memoranda dated 5/97, 10/97, and 1/98).

In addition to concluding that there is no public health problem, Dr. Jones concluded that the current labeling addresses "depression and symptoms of psychosis". The labeling addresses depression, which is a mood disorder. Psychosis is a thought disorder which interferes with the perception of reality. In addition to the wording regarding depression, the current labeling states: "The following CNS reactions have been reported and may bear no relationship to therapy - seizures, emotional instability, dizziness, nervousness, drowsiness, malaise, weakness, insomnia, lethargy and paresthesias." Thus, it would appear that psychosis is unlabeled.

Psychosis should be a labeled adverse event for Accutane. In addition to the cases reported via MedWatch, the Sponsor submitted in the briefing documents a case report describing clear positive de-challenge and re-challenge for Accutane associated psychosis. In this reviewer's opinion, this is the type of case which, even in isolation, would strongly suggest causality, as discussed above. In fact, the Sponsor states in the submission that this case implicates a causal relationship between Accutane and psychosis.

#### Review of the Psychiatric Information

Dr. Jacobs, an expert on suicide, reported his principal findings as follows:

- "Depression, suicide, and suicide attempts as reported are much less than occur in general population; far less than in high risk population (acne patients)"
- "Rechallenge data in MedWatch reports are clinically insufficient to support a diagnosis of depression"
- "The clinical phenomena of the suicides are consistent with those in the suicide literature: no evidence of Accutane effect"
- "There is no biochemical basis for isotretinoin to be associated with depression, suicide, or suicide attempts".

He then concluded that "Accutane use is not associated with depression or suicide" and that "to suggest that there is an association could lead to the erroneous belief that discontinuing Accutane therapy will treat coincident depression."

The problem inherent in basing conclusions on "observed" vs. expected rates has been discussed in the previous section. Dr. Jacobs' statement regarding rechallenge cases appears to be founded in his observation that the majority of cases did not receive treatment specifically for depression or that the reports did not contain sufficient clinical information to confirm the diagnosis of depression. It is unclear why the lack of detail inherent in MedWatch reporting is the basis for fact in the first case (did not receive specific treatment); but is a disqualifying fault

in the second (insufficient clinical detail). In addition, the majority of the cases with sufficient detail submitted for my review as 15 day reports since 1996, as well as the published cases, clearly indicate spontaneous recovery within a few days of discontinuing Accutane. It is unclear why additional therapy is considered a prerequisite for the diagnosis of a drug-induced mood disorder that resolves as described. Dr. Jacobs' point about the possible insufficiency of Accutane discontinuation is well taken and should be prominently captured in the revised labeling.

Of the seven published reports included by the Sponsor in the December submission which discussed retinoid associated psychiatric disease, all documented one or more of the problems we have targeted. For example, Duke (1993) notes 2 cases assessed as evidence of "severe psychiatric and psychological reactions to isotretinoin...recently groups of cases have appeared, suggesting that these side effects may not be the rarity they were initially considered to be...". The *Canadian Journal of Psychiatry* report by Byrne and Knatko (1995) describe 3 cases characterized by depression, anergia, headache, irritability and agitation; two were actively suicidal. None had a family history or previous psychiatric history. They state that "there may well be a specific syndrome which develops in some young people who are taking isotretinoin, and that the effect of this psychological change may be potentially life-threatening." (Dr. Byrne has a paper in press, *Irish J Psych Med*, describing 5 cases, 3 of which were suicidal; Two persisted after discontinuation; these resolved in 10-14 months with treatment. *Personal communication*). Scheinman, Peck, Rubinow, DiGiovanna, et al (1990) concluded that "depression is a rare side effect of isotretinoin...most likely represents an idiosyncratic side effect of isotretinoin rather than a predictable effect in a subset of patients predisposed to develop major depression."

X The Sponsor's submitted material states that "An evaluation of 526 cases of depression received by Roche Drug safety in association with ROACCUTAN® could not exclude a causal (emphasis added) relationship in single, predisposed |

Dr. Jacobs statement regarding the lack of a biochemical basis for an association will be discussed in the next section, since it was echoed by the third consultant, Dr. Bickers.

#### Review of Dermatologic Information

Dr. Bickers, a dermatologist, began his review by addressing the effectiveness of isotretinoin in the treatment of acne. Dr. Bickers also noted reports indicating that isotretinoin is helpful in reducing the psychological impact of severe recalcitrant nodular acne. These were not found in the supporting documentation, but the

December 8 submission by the Sponsor included a paper by Rubinow et al (*J Am Acad Derm* 1987; 17:25) which evaluated the psychiatric morbidity and mood characteristics of 72 patients with cystic acne before and after treatment with isotretinoin. This paper showed a statistically significant decrease in anxiety (no placebo or active control). Subset analyses suggested improvement in depression scores for patients with predominantly facial lesions (n=15), but there was no correction for multiple comparisons, as pointed out by the authors. In any event, the subject of concern is not situational depression, but severe psychiatric disease. In fact, the above paper showed no excess psychiatric morbidity in this population on diagnostic interviews in comparison with "normative prevalence figures". Rather, the authors state that they have demonstrated "evidence of moderate psychological distress in patients with cystic acne".

The unique efficacy of Accutane for severe nodular acne is not in question, and this information will not be further reviewed here.

Safety was addressed by noting that Accutane has a similar side effect profile to Vitamin A. Dr. Bickers listed six effects of vitamin A excess shared by Accutane, such as hepatotoxicity, pseudotumor cerebri, muscle and bone pain, xerosis, etc, then stated "no evidence of associated depression". The publication by R. Restak (*J Nervous Mental Disorders* 155:72-75, 1972) was not addressed. This publication describes, in detail, the development of a severe toxic psychotic reaction in an 18-year old patient with no antecedent psychiatric illness. The patient then went on to develop pseudotumor. Resolution of both entities occurred upon discontinuation of vitamin A. The author states that the case establishes "vitamin A as an exogenous agent capable of closely imitating primary psychiatric disease", emphasizing the continuum from a severe depressive illness without evidence of pseudotumor to the development of concomitant pseudotumor, a well established manifestation of hypervitaminosis A.

Dr. Bickers then addressed the issue raised by Dr. Jacobs and by the Sponsor regarding the lack of a biologically plausible mechanism to explain an association between retinoid use and psychiatric disease. He states that there is "no evidence that the pharmacologic effects of retinoids influence serotonergic or dopaminergic pathways in human brain."

At the time of the submission, the following references were available via medical on-line services:

- 1) Chromosomal locations and modes of action of genes of the retinoid (vitamin A) system support their involvement in the etiology of schizophrenia. Goodman AB. *Am J Med Genet* 60:335-48, 1995.

2) Congenital anomalies in relatives of schizophrenic probands may indicate a retinoid pathology. Goodman AB. *Schizophr Res* 19:163-70, 1996.

3) Induction of adenylyl cyclase sensitive dopamine D2-receptors in retinoic acid induced differentiated human neuroblastoma SHSY-5Y cells. Faronqui SM. *Life Sci* 55:1887-1893, 1994.

4) Effects of retinoic acid on NB69 human neuroblastoma cells and fetal rat mid brain neurons. Mena MA et al. *J Neural Trans* 8:85-97, 1994. (This paper demonstrates detrimental effects of RA on catecholamine neurons despite its probable positive trophic effect on the differentiation of immature cells to cholinergic neurons.)

Subsequent to the submission, a paper was published by Pierre Chambon's group (*Science* 1998;279:863) demonstrating in adult murine brain that retinoid receptors are involved in the regulation of brain functions. These authors also suggest that retinoic acid signaling defects may contribute to pathologies such as Parkinson's disease and schizophrenia.

While none of these papers in isolation establishes the role of retinoic acid in the regulation of adult human brain function, they appear to be strongly suggestive of a biologically plausible mechanism. Given the well established correlation between findings of this nature in murine and human brain (Dr. Stephen Goldman, personal communication), the *Science* paper, in particular, clearly supports involvement of retinoic acid in dopaminergic signaling.

Dr. Bickers concluded: "in my opinion, isotretinoin can prevent or diminish the severity of depression, psychosis, suicide and suicide attempts."

## Conclusions

The psychiatric adverse events described in the submitted line listings and summaries are consistent with the data I have received via MedWatch serious event reports (see previous three review memoranda and Pharmacovigilance consult, appended). Many of these reports, as well as the published cases, describe irritability or uncontrolled anger, headache, fatigue, and severe depression, some with suicidal ideation or action. A few case reports also note hallucinations (visual where specified) or other symptoms of psychosis.

The rapid resolution noted in many of the reported dechallenge cases suggests that an educational message to practitioners and their patients may prevent significant morbidity, and hopefully, mortality.

Other CNS adverse events noted in the 15 day reports I have reviewed include sudden sensorineural hearing loss with positive dechallenge (unlabeled), stroke/CVA (including reports in young males obviously not confounded by oral contraceptives; unlabeled), convulsions (labeled), and pseudotumor cerebri (labeled). Given all the pieces of evidence available, it is difficult for me to avoid the conclusion that Accutane can adversely affect the adult human brain in clinically significant ways and that Accutane use is associated with severe psychiatric disease in some patients.

The reported effects on the CNS are not surprising given the the profound effects of the drug on the integument, and the common origin of the brain and skin from the neural crest. The emerging science linking retinoid receptor biology with dopaminergic regulation may ultimately inform an understanding of the neural pathways altered by exogenous retinoid administration and provide support for causality. The validity of such a conclusion would be greatly enhanced by more detailed reporting of psychiatric adverse events in patients taking Accutane.

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Copy of Pharmacovigilance memorandum follows: