A number of retinoids have been synthesized. All these substances are vitamin A derivatives. Four isomers have been fully developed:

* Tretinoin which is on the market in a number of countries as a topical drug for the treatment of mild to moderate acne. It is an effective drug which is used by a number of dermatologists.
* Isotretinoin has been first studied in the United States for the treatment of disorders of keratinisation. In 1979, Peck issued a publication describing the drug as extremely effective in the treatment of severe cystic acne. The development in the indication “acne” was initiated and the drug was first introduced in the U.S. in 1985.
* TIGASON, OR TEGISON in the United States, is a retinoid ethylamide, etretinate, for the treatment of disorders of keratinisation.
* It is now replaced or soon will be replaced by acitretin or NEOTIGASON which is the main metabolite of etretinate. It was believed initially that acitretin would have the advantage of a much shorter half life of elimination, which would allow a short duration of the post-therapy contraception time. Unfortunately and for reasons which will be discussed later, this advantage could not be confirmed.

These retinoids are on the market for the treatment of two groups of indications:

* on the one hand the aromatic retinoids, TIGASON (etretinate) and NEOTIGASON (acitretin) for the treatment of severe forms of psoriasis and disorders of keratinisation, pityriasis rubra pilaris, Darier’s disease, lichen planus, ichthyosis and palmo-plantar keratoderma.
* on the other hand, ROACCUTANE (isotretinoin) is most effective in the treatment of severe cystic acne and acne resistant to conventional medications.

Retinoids have been used in a relatively limited number of patients in further indications namely:

* precancerous lesions of the skin and mucosae. So far the retinoids have not offered any significant advantages over conventional therapy.
* interesting results in the form of an extension of the survival time have been obtained with ROACCUTANE in children with neuroblastoma.
* promyelocytic leukemia, a very interesting indication for tretinoin or all-trans retinoic acid given orally. An important percentage of successes has been observed in this indication.

With the exception of the latter-an-oral formulation of all-trans retinoic acid has been introduced in some countries for the treatment of promyelocytic leukemia - these oncological indications necessitate further research on large groups of patients in order to be fully documented.

The considerable clinical experience collected with retinoids as well as the data available from the literature fully document their effectiveness. It is certainly important to have a full knowledge of their effects. However, it is essential as well to have a complete knowledge of their potential side effects.

A study of the frequency of the side effects spontaneously reported to Roche since the introduction of the drug illustrates that a correct prescription of Roaccutane may, to a certain extent avoid these side effects. The internal data collected by the manufacturer indicates that, as the drug was progressively introduced in most countries in the world, the frequency of the side effects reported increased up to a maximum which was reached in 1987. At that time, the drug had been made available in almost every market. Due to this increased frequency, Roche intensified the diffusion of the messages to the medical profession regarding the tolerance to the drug and made the messages more specific and acute. As a result, the frequency of the side effects spontaneously reported decreased progressively, an evolution which demonstrates that a better and largely disseminated knowledge of the rules for the prescription produces improved tolerance of the drug. Clearly, Roaccutane will further induce side effect in a number of patients. However, on the one hand these side effects may sometime be predicted in some patients at risk (diabetes or obesity for instance), on the other hand their frequency and severity can be reduced to an acceptable minimum if some rules are strictly followed.

Most of these side effects are known because they represent manifestations of a hypervitaminosis A, namely:

* dryness of the skin and mucosae are the most
common side effects. Cheilitis is present in almost every patient. It has even been considered as a marker for the intake of the drug; a patient who does not present with cheilitis is not taking the drug. Conjunctivitis presents a very frequent effect. Patients wearing lenses should be recommended to switch to glasses in order to avoid aggravation of the symptoms.

* increased pressure of the cerebro-spinal fluid (pseudo-tumor cerebri) is a frequent side effect which is observed mainly with high doses of ROACCUTANE for the treatment of conditions other than acne. It is well-known as well with the tetracyclines. This is the reason why concomitant administration of ROACCUTANE and tetracyclines should be avoided. Other side effects listed here are more episodic or even anecdotal.

Until recently, these side effects were difficult to classify. Saurat in Geneva has proposed an interesting classification in which he distinguishes between:

* pharmacological side effects, which are related with the pharmacological properties of the drug. These effects are therefore predictable. They are frequent and mostly dose-related, which implies that if the dose is reduced, the frequency and the intensity of the effect will decrease. Last but not least, they are reversible upon adaptation of the dose or discontinuation of treatment.

* toxic side effect are of more concern because they reflect a toxic effect of the drug observed in a predisposed patient, i.e. in patients with a chronic or intercurrent disease such as hepatic, renal or metabolic disfunction or disease (diabetes, alcoholism, hepatitis, obesity).

They are difficult to predict.

They may depend on the cumulative dose of the drug and it is therefore essential to carefully adapt the dose to the severity of the condition and to the clinical effect, always trying to give the smallest possible dose.

They are not always completely reversible as for instance the side effects on the bones: radiological alterations induced by the retinoids are not reversible.

Last but not least, they may affect organs or systems on which no effect of the drug is expected, such as the liver: retinoid hepatitis has been observed in alcoholics or in patients with a history of chronic hepatitis.

In the daily practice, two categories of side effects should be the main concern for the dermatologist, namely the effects on the blood lipids or those on the bones.

As far as the side effects on the lipids are concerned, the retinoids can induce serum lipid or triglyceride elevations. It is therefore essential:

* to obtain a differential check performed by means of a precipitation technique for the various lipid fractions. The ratio total cholesterol/HDL is important as far as possible atherogenesis is concerned and should be below 4.5. The normal HDL levels are 0.45 g/l in males and 0.55 g/l in females. In practice, it can be considered that levels below 0.35 g/l are atherogenic.

* to check the lipids and the triglycerides before treatment in order to have baseline values and ensure correct further biological monitoring, also to detect a possible, still unknown, alteration of the lipid profile. A few examples of still unknown familial hypertriglyceridemias in young patients with acne have been detected on the occasion of these systematic checks before treatment.

Values above twice the normal values should be considered a contraindication and these values should be normalized possibly through adequate diet and medical treatment before administration of Roaccutane.

* to repeat the check after 2 weeks of treatment.

Should the values be normal, no further check is necessary.

Should the values be abnormal, then adequate therapeutic options (diet, hypolipaemic agents) should be instituted in an attempt to bring the values back to normal. Should the values still be raised despite the associated treatment, then the retinoid should be stopped.

* to advise the patients refrain from alcohol and, eventually to combine the retinoid (Tigason, Neotigason or Roaccutane) with a lipid lowering agent such as gemfibrozil or eicosanoic acid derivatives (fish oil supplementation) in order to possibly avoid these alterations of the lipid profile.

Pre-existing high, stable VLDL values associated with low HDL values before treatment are basically a contraindication to retinoid-therapy, unless the values can be brought to baseline through adequate diet and
medical treatment.

The side effects on the bones have been observed mainly in patients receiving high doses of Roacutane for the treatment of conditions other than acne (initially, clinical trials have been made with isotretinoin in the treatment of severe disorders of keratinisation such as psoriasis, Darier, lichen planus or ichthyosis, indications in which high doses of Roacutane must be given; 1-2 mg/kg/day over prolonged periods of time in order to obtain efficacy. In Europe where doses of 0.5 - 1.0 mg/kg of Roacutane are normally given, these side effects on the bones are rare, especially if the concept of the cumulative total dose (which will be developed later) is being followed.

The ossification disorders in the form of ossifications of the tendons and/or ligaments may occur with Tigason or Neotigason as these drugs are given over long periods of time for the treatment of disorders of keratinisation. In most cases, these ossification disorders are totally asymptomatic and the patients do not complain. Therefore, it is important to be aware of their possible occurrence and the following precautions and recommendations can be made: * a control X-ray (baseline X-ray) should be considered whenever long term treatment is planned and should be repeated at yearly intervals.

* Should a patient complain about muscular or articular pain during treatment, a radiological control of the corresponding area should be obtained. Scintographic examination is of little diagnostic value for these ossification disorders, since the hyperactivity observed is not specific.

* In order to limit as much as possible the exposure to X-rays, the following radiological programme is recommended:
  - cervical, thoracic and lumbar spine, lateral view, one sided
  - knee (right or left), lateral view, one sided
  - ankle (right or left), lateral view, one sided
  - both forearms, front view.

The main practical problem with Roacutane as well as with the other retinoids is clearly the teratogenic potential of these drugs.

Isotretinoin

The vitamin A derivatives are highly teratogenic and include severe malformations of the foetus when given to pregnant females. This potential is maximal at a very early phase of the pregnancy, during the first weeks. It is therefore of major importance before making the decision to treat females of childbearing potential with a retinoid to exclude a per-existing pregnancy. Clearly, it is mandatory to avoid pregnancy during treatment as well as after treatment when the drug is still present in the body.

The existence of blood levels of the retinoid depends very much on the metabolism and elimination of the active substance, i.e. upon its half life of elimination. Isotretinoin is rapidly eliminated from the body and is not stored in any deep compartment. The half life of elimination is short and it has been shown that it is approximately two days. Therefore the post therapy contraception time for Roacutane is limited to 1 month.

As acne is a disease which affects mainly children or young adults, the teratogenicity of Roacutane represents a major concern for Roche and should be a major concern for the prescribing physicians and for the patients. A very thorough and detailed campaign of information, emphasizing the mandatory precautions in female patients of childbearing potential, has been organized by Roche. This campaign has been heavily supported by the Health Authorities in every country.

Despite these efforts, the precautions are not always being followed and a number of malformed children born from mothers who inadequately took the drug have been registered in the Drug Safety Data Base organized by the manufacturer: up to October 1993, a total of 133 malformed children (babies, stillborn babies or foetuses investigated after spontaneous or induced abortion) has been recorded. Therefore, all efforts should be made, and are being made to adequately inform all those concerned. The following precautions must further be emphasized as broadly as possible:

* Should a pregnancy occur during treatment or one month after its discontinuation, there is a major risk of malformation of the foetus.
* Pregnancy should be excluded before administration of Roaccutane in every female patient of childbearing potential.
* Pregnancy must imperatively be avoided during the entire duration of treatment. Every female patient
of childbearing potential must imperatively follow a permanent and effective contraception during treatment and for at least one month after discontinuation of the administration of the last dose of Roaccutane.
* Should for some reason an effective contraception be contraindicated or not be possible in a female patient, the administration of Roaccutane is contraindicated as well.
  * Oral contraception should be preferred whenever possible, at least in young patients.
  * The patient should be fully informed about the precautions and the risks connected with the administration of Roaccutane.

Acitretin and etretinate

The problem is different as far as etretinate is concerned. As an ethyl-ester, the substance is stored in a deep compartment in the body from where it is released progressively; the half life of elimination is 120 days and blood levels of etretinate can be detected in the blood as long as several months or in some patients over a year after discontinuation of the administration. Therefore, pregnancy must be avoided for two years after discontinuation of the treatment.

Acitretin, the active substance of Neotigason is an acid. When Tigason is administered, the active substance etretinate, which is pharmacologically inactive in man, is rapidly hydrolysed into acitretin. It has been considered initially that the conversion from etretinate to acitretin is irreversible.

As an acid, acitretin is not stored in a deep compartment and has a relatively short half life of 2 days as compared to etretinate. Therefore, it was believed initially that a shorter post-therapy contraception time of 2 months could be recommended in female patients of childbearing potential treated with Neotigason. Such a shorter contraception time would definitely represent a major advantage for Neotigason.

Unfortunately, further metabolic data has demonstrated that a retroconversion of acitretin into etretinate is possible and occurs in a limited number of patients, mainly under the influence of alcohol. So far, it is not possible to identify before treatment those patients in whom this reaction will occur. Therefore, as etretinate may be present in the serum of these patients, the post-therapy contraception time with Neotigason had to be extended to 2 years.

As the retroconversion of acitretin occurs in a limited number of patients taking alcohol during treatment, it can however be considered that Neotigason is safer than Tigason as far as teratogenicity is concerned, provided that the female patients of childbearing potential refrain from taking alcohol.

With a different time frame (2 years instead of 2 months) the same limitations and precautions as in the case of Roaccutane are valid for Tigason and Neotigason.

As already mentioned above, the dosage rules represent an important issue with the retinoids since most of the side effects of these drugs may be avoided if the dosage is carefully adapted. These rules are different for each retinoid and must be considered individually for Tigason, Neotigason or Roaccutane.

The dosage rules for Tigason are complex:
  * the dosage has to be adapted individually, on body weight basis and according to the type of keratinisation disorder treated. Pustular disorders of keratinisation can be started on 1.0 mg/kg/day, this dosage being adapted after two weeks, according to tolerance, clinical efficacy and association with other therapeutic means such as PUVA or UVB. Radiation therapy combined with Tigason allows half the dose of both Tigason and irradiations in a large majority of patients.
  * An initial daily dose of 0.5 mg/kg/day must be preferred in ichthyosis, psoriasis vulgaris or lichen ruber planus, this initial dosage being adapted after 2 weeks.
  * Severe flare ups of erythrodermic psoriasis have been reported with an initial dosage of 1.0 mg/kg/day. Therefore, in this indication, the initial dosage should be limited to 0.3 mg/kg/day, in order to assess the tolerance of the drug.

A considerable simplification of the dosage rules can be achieved with Neotigason:
  * The daily dosage is no longer calculated on body weight basis but simply on daily dosage. This dosage is independent of the indication.
  * The daily dosage must be adapted individually after 2-3 weeks according to tolerance, efficacy and combined treatment (PUVA)
  * The initial dosage for every patient is 25 mg (one
25 mg capsule) or 30 mg (three 10 mg capsules) per day.
* Dosages of more than 70 mg/day should not be given as the frequency of side effects increases while the efficacy of such high doses could not be demonstrated.

In the case of Roaccutane, the dosage rules are as follows:
* Treatment should be started with 0.5 mg/kg/day. Higher doses of 1 mg/kg/day or less may be given in extremely severe cases. They should nevertheless not be given over prolonged periods of time.
* As shown by several studies on large groups of patients (Lehucher-Ceyrac et al, Harms, Layton et al.) the occurrence of relapses does not depend on the daily dose but rather on the total cumulative dose i.e. the daily dose x number of days of treatment.

Whenever a total cumulative dose corresponding to less than 100 mg/kg is administered the frequency of relapses is high (40-80%). If the total cumulative dose is above 100-120 mg/kg, relapses become much less frequent (10-20%).

Therefore, a total cumulative of 120-150 mg/kg, given in one or several courses of treatment ensures the lowest possible frequency of relapse.

* Whenever a total cumulative dose of 120 mg/kg has been given without a satisfactory clinical result, i.e. if the acne persists, administration of a higher dose is not indicated as the acne appears no longer as a disease per se but as a symptom of another intercurrent disease (polycystic ovary, endocrinological disorder, toxic acne) necessitating other therapeutic measures (surgery, hormonal treatment).
* Should a relapse in the form of a severe acne (grade 2 or more) occur after some time in a patient having received a total cumulative dose of 120-150 mg/kg, a second course of treatment according to the same rules should be considered.

The selection of an appropriate contraception in female patient is of paramount importance. Whenever possible, it should follow these rules:
* In women of childbearing potential, a retinoid should not be administered without an effective contraception. Statements made by the patients regarding continence should be considered with extreme care.
* Whenever possible, oral hormonal contraception should be preferred to the local contraceptive methods.

* In female patients below 25 years of age: no contraindication exists, oral contraception should be recommended in the form of a low-dosed estrogen-progestagen third generation combination.

Should the patient present with a virilisation syndrome, an endocrinological check-up should be performed and contraception with cyproterone acetate should be preferred.

If a contraindication to oral contraception exists, promestrone, nomegestrol, chloramadinone acetate or an I.U.D. should be preferred. A specialist’s advice should be requested.

* In female patients 25-40 years of age: in absence of contraindication, oral contraception should be recommended in the form of a low-dosed estrogen-progestagen third generation combination.

If a contraindication to oral contraception exists in annullipara, an endocrinological as well as a check-up should be performed and contraception with cyproterone acetate should be preferred.

If a contraindication to oral contraception exists in a multipara, an endocrinological as well as a check-up should be performed, a specialist’s advice should be requested and promestrone, nomegestrol, chloramadinone acetate or an I.U.D. should be preferred.

* In female patients of childbearing potential above 40 years of age, and/or when the risk of being pregnant can be secured as minimal, contraception with an I.U.D. can be regarded as sufficient.

As the retinoids must always be combined with oral contraceptives in female patients of child bearing potential and as they may be prescribed in patients with chronic intercurrent diseases, it is important to briefly consider the potential interactions between the retinoids and other currently used medications. The following statements and recommendations can be made in this connection.

* Combination between a retinoid with vitamin A or a drug containing vitamin A should be prohibited since the risk of hypervitaminosis A would increase dramatically.
* Combination of a retinoid with a tetracycline
should be avoided since both tetracyclines and the retinoids may increase the intracranial blood pressure (pseudo tumor cerebri in the U.S. terminology).

* Etretinate, which is strongly bound to serum proteins, may displace the antiepileptic drugs from their protein bindings (at least theoretically). Furthermore, isotretinoin reduces the absorption and increases the clearance rate of carbamazepine. Finally, phenobarbital accelerates the biotransformation of isotretinoin.

In epileptic patients, low doses of the retinoid should therefore be given initially in order to assess the tolerance of the drug. Similarly, the dosage of the antiepileptic treatment should be adapted in order to avoid the occurrence of an attack.

For these reasons, retinoid treatment in an epileptic patient should not be regarded as a routine treatment and should be started in hospital in close collaboration between the dermatologist and the neurologist.

The retinoids are highly potent drugs. Whereas Tigason and Neotigason are most effective, they represent a symptomatic treatment which relieves the symptoms but does not cure the disease. Roaccutane is different in this connection: it is the only therapeutic possibility in severe forms of acne which so far could not be treated by other means. Furthermore and due to its well elucidated mechanism of action, isotretinoin is an etiological treatment of acne: it alleviates the pathogenic mechanisms of the disease, namely the increased sebum excretion, the inflammation, the infundibular hyperkeratinisation and the superinfection with P. acnes.

The selection and management of the patients is a difficult process which requires experience, knowledge of both the drug and the disease and a close collaboration with the patient. The decision to treat a patient with a retinoid must be made on a step by step approach which can be summarized, as follows:

* What should be treated: for such potent drugs as the retinoids, it is essential to make an exact diagnosis, to assess the severity, the extension and the implications of the disease and to assess the risk-benefit ratio. Whereas this may be easy in the case of acne, it might be more difficult in the case of the disorders of keratinisation, when a number of differential diagnoses should be taken into consideration. This is one of the reasons why the prescription of the retinoids is restricted to dermatologists in most countries.

* Who should be treated: very strict inclusion and exclusion criteria such as age, sex, previous treatments applied, concomitant diseases must be taken into consideration in the decision making process. As the rules for administration are strict, the patient must strictly follow the recommendations of the treating physician in order to obtain the best possible therapeutic result. Therefore, patient compliance and readiness to co-operate play a major role.

* How to treat: it is a difficult and time consuming task for the physician to properly inform his patient and to establish the conditions of the treatment dosage, combined treatment, regular but adequate clinical and biological monitoring limited to those parameters which are of paramount importance for a given patient in order to limit the costs.

Such a stepward approach should be systematic and is valid for every patient for whom treatment with a retinoid is justified.

The retinoids have opened a new era in the therapeutic possibilities for a number of severe dermatological diseases. After several years of use, these drugs are now well documented in the literature and considerable clinical experience is available from many experts.

The present status of the retinoid therapy can, as in the case of depression, be illustrated with an iceberg. An important emerging part is well explored as attested by the excellent efficacy and tolerance of these drugs when they are adequately prescribed. However, a major, still submerged part of the iceberg needs to be further explored. A number of most fascinating aspects need further investigation: pharmacokinetic profile, mechanism of action for the aromatic retinoids Tigason and Neotigason, identification and localisation of specific receptors, role of the retinoids as prophylactic or therapeutic agents for oncological diseases, further formulations in order to improve efficacy and safety. The future answers to some of these questions will most probably allow identification of other derivatives with a more specific effect on certain target organs and with improved safety. The teratogenicity of these drugs raises a number of daily problems and should represent a challenge for further research.