Comparative analysis between Tretinoin (anti-cancer) and Isotretinoin (anti-acne)

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Open source

(extract and provisional version)

Year: 2020

Thanks :

Thanks to Nathan C. Carr, author of the following document:

https://www.pdffiller.com/101004448-Accutane-Report-June-2009-01cipdf-Hoffmann-La-Roches-Cover-up-of-Accutane-By-Nathan-C-Carr-

This pdf is largely inspired by it, it is a verified summary, sourced and reformatted part of his analysis.

"Science without conscience is nothing but the ruin of the soul"
Rabelais

"Even under duress, I will not use my knowledge against the laws of humanity.
I will inform patients of the decisions being considered, their reasons and their consequences.
I will never deceive their trust and harness the power inherited from circumstances to force the conscience "
Hippocratic oath

Contents :

Glossary :

DNA: Acid in the nucleus of living cells, an essential constituent of chromosomes and carrier of genetic characteristics.

Apoptosis: Physiological process of programmed cell death.

Chromosome: Chromosomes are made up of DNA that carries the genes (25,000 about)

Enzyme: An enzyme is a protein that catalyzes a biochemical reaction.

Isomerization: in chemistry, transformation into an isomeric compound which is formed from same elements in the same proportions, but which has properties different

Metabolization: in physiology, biochemical transformation of a substance into a living organism during metabolism.

Mitosis: Division of the cell during which each chromosome splits.

Senescence: biological aging process resulting in stopping irreversible cell cycle resulting in cell death. After a certain number divisions, cells end up not reproducing and die.

Telomerase: the enzyme in a eukaryote that repairs telomeres on chromosomes so that they do not become progressively shorter in successive cycles of chromosome replication.

Telomere: End of a chromosome.

Abstract :

During acne treatment with isotretinoin, ¼ of the usual dose is metabolized
anti-cancer chemotherapy (acute promyelocytic leukemia (APL)).

We may wonder how to explain that the side effects would be of
100 times to 1000 times less important according to the instructions for the two drugs with
only 4 times less metabolized Tretinoin?
And this in contradiction with the fairness of the many testimonies.

The anti-cancer effect of tretinoin consists of shorter telomeres in the
cells, they approach the Hayflick limit and cannot divide and
proliferate as much as before being damaged.
They then undergo growth arrest and cell death (apoptosis).

If Isotretinoin really causes telomere shortening and regulation
to the drop in the enzyme telomerase, this could mean huge implications
significant in order to maintain adequate cell proliferation throughout the body
for the rest of a former patient's life.

Contrary to what the leaflet claims, this drug is found to have a latent effect
chronic on people's bodies.

Before and after treatment studies should be carried out on a larger scale by carrying out
tomograms of the hippocampus and the subventricular area of the brain.

A telomere length test before and after treatment on a cohort of patients
robust would make sense.

A specific study of tissue biopsies of different organs and tests
blood before and after treatment with Isotretonin could identify in which
how much cell division has been reduced.

Introduction:

Isotretinoin, a controversial anti-acne drug, is believed to be responsible for many deaths by suicide and chronic illnesses that resemble a diffuse spectrum of syndromes autoimmune poorly studied to date.

This isotretinoin intolerance syndrome does not occur in all patients, but can, however, reach very serious forms, and chronic victims represent a non-negligible percentage of patients, victims most of the time subjected to long medical wandering.
Indeed, this syndrome is not mentioned at all in the instructions, despite its reality dramatic.

We will see that isotretinoin is metabolized by isomerization to tretinoin, a anti-cancer molecule used in acute leukemia. The effects are almost the same but with different intensities and frequencies.
However, they appear to be largely underestimated for isotretinoin, probably in because of mercantile factors.

1. Interconversion between Tretinoin (anti-cancer) and Isotretinoin (anti-acne):

Extract from the instructions for PROCUTA 20 mg, soft capsule:

"5.2. Pharmacokinetic properties:
Biotransformation:

The transformation of isotretinoin into tretinoin (all-trans retinoic acid) being a reversible reaction (interconversion), the metabolism of tretinoin is by therefore linked with that of isotretinoin. It is estimated that 20% to 30% of the dose of isotretinoin is metabolized by isomerization. " **[1]**

Roaccutane = Isotretinoin
Versanoid = Tretinoin

So 40 mg of Isotretinoin converts between 8 and 12 mg of Tretinoin

The package leaflet for Vesanoid (tretinoin) indicates an incidence of depression of 10 to 29%. **[2]**

Regarding Isotretinoin (Roaccutane), this rate of depression is divided by 100 and becomes "very rare": 0.0001% to 0.001%. **[3] [1]**

We find the same difference from "very common" for Tretinoin (Vesanoid) to "very rare ”for Isotretinoin (Roaccutane) most of the effects complained of by chronic victims of isotretinoin (Inflammatory bowel disease, alopecia, hypersudattion, etc ...).

How to explain such a discrepancy in pharmacovigilance reports (in comparison testimonials, and other independent studies on isotretinoin)?

For a man of 80 kg:

The usual average isotretinoin dose is between 0.5 and 1 mg / kg / day **[1]** , i.e. a dose between 40 and 80 mg per day.
So 10 to 20 mg of tretinoin will be metabolized.

The usual average dose of tretinoin is 80 mg. **[4]**

So, for the same person, the dose of tretinoin will be 4 times less in the treatment of acne with isotretinoin (20 mg), than during anti-cancer treatment (80 mg).

So how to explain that the side effects would be 100 times to 1000 times less

important according to the two leaflets of the two drugs with only 4 times less metabolized tretinoin?
It is an isomer, therefore the same molecule but with different properties.
To what extent exactly?

The fact remains that **during an anti-acne treatment, ¼ the usual dose of anti-cancer chemotherapy** (Vesanoid is prescribed for acute promyelocytic leukemia (APL)) **[4]** .

2. Comparative analysis of the 2 molecules:

Isotretinoin suppresses cell division in the hippocampus. **[5]**

However, Tretinoin downregulates the enzyme telomerase and induces telomere shortening and cell death **[7]** .

Isotretonïne degrading into Tretinoin would therefore cause by analogy a shortening of telomeres leading to cell division which will be definitely discontinued earlier compared to its theoretical proliferation.

There is a limit on the number of times a cell can divide.
This is called the Hayflick limit (see *figure 1* below).

Figure 1: Hayflick limit

Indeed, the telomere shortens a little each time a cell divides, and therefore this sets a limit on the number of times a cell can replicate, known as Hayflick limit name. then the cell stops dividing and suffers cell death programmed (apoptosis).

Hayflick limit can be seen as a countdown mechanism cell in order to specifically protect us from cells that reproduce from

uncontrollably (as in the case of cancers).

However, there is a specialized enzyme called telomerase that works to repair damage to telomeres, in order to maintain their stability and lengthen them, thus overcoming the Hayflick limit.

Telomerase is by nature more expressed in the cells of the body which renew more often and have the fastest divisions: the system immune system, skin, bones, digestive tract, mucous membranes, etc.

However, these are precisely the organs most affected in the reports of pharmacovigilance concerning isotretinoin.

For patients on Isotretinoin, there might be too few divisions cellular or sometimes not at all because Isotretinoin would have caused a critical shortening of telomeres, leading to growth arrest and death cellular or cellular senescence in various areas of the body where the proliferation cell phone is supposed to continue.

And that would change the way cells read their genes (transcription of protein). This is why Isotretinoin is said to have an extremely long list of effects. secondary involving all tissues and organs of the human body.
The cells most vulnerable to this effect are those which must divide and proliferate (undergo mitosis) more often.

This is how isotretinoin would reduce acne by destroying the sebaceous glands, and why in some cases the acne does not come back and the patient ends up with skin dry, dry mucous membranes, digestive problems, hair loss and other effects secondary.

During and after treatment, Isotretinoin would increase cell division and the rate of cell renewal (new cells are born and die more quickly), and therefore these cells would run out of cell divisions sooner and would be pushed into their Hayflick limit.
This would also explain the time lag between the taking and the onset of effects. disabling secondary.

This can be illustrated by observing what happens when someone eats liver polar bear which contains extremely toxic levels of vitamin A.

The leaflet for isotretinoin says that all side effects suggestive of of hypervitaminosis A were spontaneously reversible after discontinuation of isotretinoin **[3]** in rats heavily exposed for more than two years (at dosages of 2, 8 and 32 mg / kg / day) consisted of partial hair loss and increased plasma triglycerides.
Yet many patients exposed to isotretinoin are chronically ill Consequently.

3. Research avenues:

This analogy between Isotretinoin and Tretinoin deserves to be fully verified.
This is because no one would want to maintain a drug that causes some form of premature and insidious aging in millions of adolescents and young adults suffering from acne.

Specialized tests are available to assess telomere shortening,
this would validate the damage caused by Isotretinoin.
One of them is called the DNA *terminal* restriction *fragment* **test** or the DNA **test. telomere length (TTAGGG sequence)** .
A test before and after treatment on a cohort of patients would be very judicious.

It is imperative to understand that stopping Isotretinoin does not necessarily mean that its effect wears off.
There are a large number of reports from people who claim that some of their side effects, especially the worst types, did not appear until years later have stopped isotretinoin.
According to FDA data, inflammatory bowel disease and depression are still present 20 years after the treatment (with gradually a first place for various intestinal disorders, supplanting depression and suicides). **[6]**

This drug is therefore shown to have a **chronic latent effect** on people's bodies, which which also cured their acne, with a lot of collateral damage.

Retinoids downregulate telomerase and telomere length in a distinct pathway of leukemic cell differentiation.

In this study **[7]** , the cells that the researchers tested came from lines cancer cells, but if Tretinoin causes these effects in the blood cancer cells, then it is highly likely that it will do the same to our body's own rapidly dividing and proliferating cells, such as bone, skin, digestive tract and even the hippocampus and the subventricular area of the brain.

Every time a cell divides, the telomeres get shorter. When they become too short, the cell can no longer divide and becomes inactive or "senescent" or dies.
This process is associated with aging, cancer and an increased risk of death.
So telomeres have also been likened to a fusible bomb.

The explanation of the mechanism of action probably involves the reverse transcriptase of human telomerase (hTERT), the main regulator of cell division in our rapidly dividing cells.
Retinoic acid has already been shown to downregulate hTERT in cells cancerous, which is more than enough to call for an investigation into its effects on hTERT in human leukocytes, enterocytes, keratinocytes, sebocytes, cells endothelial progenitors and other various progenitor cells.

A specific study of tissue biopsies and blood tests before and after a
treatment with Isotretonoin could identify the extent to which cell division
has been reduced.

Conclusion:

We have observed that during anti-acne treatment with isotretinoin, we metabolize
¼ of the usual dose of anti-cancer chemotherapy (acute promyelocytic leukemia
(LAP)).
We may wonder how to explain that the side effects would be of
100 times to 1000 times less important according to the instructions for the two drugs with
only 4 times less metabolized Tretinoin?
And this in contradiction with the many testimonies.

If the cells have shorter telomeres, they get closer to the Hayflick limit
and cannot divide and proliferate as much as before being damaged.
They then undergo growth arrest and cell death (apoptosis).

If Isotretinoin really causes telomere shortening and regulation
to the drop in the enzyme telomerase, this could mean huge implications
significant in order to maintain adequate cell proliferation throughout the body
for the rest of a former patient's life.

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chronic latent on people's bodies.

Before and after treatment studies should be carried out on a larger scale by carrying out
tomograms of the hippocampus and the subventricular area of the brain.
A telomere length test before and after treatment on a cohort of patients
robust would also be very useful.

A specific study of tissue biopsies of different organs and blood tests
before and after treatment with Isotretonin could identify the extent to which
cell division was reduced.

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