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Is there evidence supporting the Cuban treatment for retinitis pigmentosa ?

Information Monitoring Summary

Documentary research

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September 13th, 2010

Notice to readers

The information in the following pages is not intended to be an exhaustive review of the literature. The goal was to make directly relevant selected information more readily available. Accordingly, not all articles or documents dealing with the topic have been reviewed.

Is there evidence supporting the Cuban treatment for retinitis pigmentosa?

Summary

Retinitis pigmentosa (RP) is a heterogeneous group of chronic, progressive genetic vision disorders [1; 14; 22]. It causes gradual deterioration of photoreceptor cells in the retina, mainly affecting the rods, which are responsible for night vision [14]. Gradual loss of the peripheral visual fieldoccurs until only central vision remains, followed by cone degeneration which may eventually result in total blindness.

Treatment in Cuba for RP patients comprises eye surgery, ozone therapy, electrostimulation and drugs [6]. In 2009, initial treatment of RP involved three weeks' hospitalization and apparently cost just over $10,000; each subsequent six-monthly ozone treatment was costing around $4,900 [20]. According to the Cuban physicians, the goal of the procedure is to increase blood flow in the degenerating portion of the retina and thereby stabilize the disease [6; 10]. However, according to l'Association des médecins ophtalmologistes du Québec, the scientific claims on which this treatment is based are erroneous, because retinitis pigmentosa is a cellular disorder unrelated to blood circulation [20]. Moreover, post-operative complications have been reported in the literature. As regards ozone action, its mechanisms and effects are neither clear nor fully understood at the theoretical level.

A Cuban study has concluded that ozone treatment is worth administering at six-monthly intervals to patients in the early stages of RP [8]. However, no longitudinal studies have been published about the long-terms effects of repeating this treatment every six months. In addition, these conclusions are based purely on visual field measurements, which are subjective. The fact that no objective measurements have been conducted using an electroretinogram substantially weakens the study's validity. The study results were published in *Ozone: Science & Engineering*, which is not a *medical* scientific review. However, critical review and analysis by peers, e.g. independent, impartial retina specialists, are key in establishing the acceptability of a study and ensuring the advancement of science. No independent studies have demonstrated that the Cuban treatments improve or stabilize retinal function in the long term [3; 11; 12]. Berson et al. (1996) even suggested that these interventions could aggravate the disorder.

Because the Cuban protocol has not been subject to critical analysis, many major authorities in the ophthalmologic field, including the Canadian Ophthalmological Society, l'Association des médecins ophtalmologistes du Québec, the RP Research Foundation in Canada and the Foundation Fighting Blindness in the U.S., as well as various authors and researchers, are questioning these treatments or regard them as pointless [4; 5; 13].

1. Retinitis pigmentosa

Retinitis pigmentosa (RP) refers to a group of chronic and progressive vision diseases, which tend to run in families, associated with different phenotypes and defects in many genes [1; 14; 22]. Among the causes are defects in visual pigment, in photoreceptor proteins or in enzymes involved in visual transduction [13]. RP affects about 1 person in 4,000 [13; 14]. It causes progressive degeneration of the photoreceptor cells in the retina, affecting mainly the rods, which almost entirely responsible for night vision. In some types of RP, the cones may also be affected. Signs and symptoms usually appear in childhood, but severe vision problems do not usually develop before adulthood. The earliest symptoms tend to be increasing difficulty seeing at night or in dim light conditions, followed by loss of peripheral visual field, which worsens over many years until only central (tunnel) vision remains [1]. This condition may ultimately lead to vision loss, though not usually total blindness.

While the defective gene has been identified for certain types of RP, the exact mechanism of cell dysfunction, damage and death is not fully understood at the cellular level [22]. Various clinical trials have been conducted to pinpoint effective treatment modalities, but none have been conclusive [3; 21].

2. Cuban protocol

Since 1992, a protocol has been offered at the *Centro Internacional de Retinosis Pigmentaria Camilio Cienfuegos* in Cuba for people with retinitis pigmentosa [6]. These treatments are also available to foreigners through medical tourism at the International Ozone Therapy Clinic [17]. The protocol involves eye surgery, ozone therapy, electric stimulation and drugs.

Surgery is performed on each eye under general anesthetic. It involves implanting a pedicle flap of retrobulbar fat with blood vessels, under the sclerosed portion, , in order to bring additional blood produced by the transposed vessels to the suprachoroidal space. The goal is to eventually increase blood flow in the deteriorating portion of the retina and thereby stabilize the disease [6; 10]. The procedure is based on the hypothesis that for its metabolic needs, the fovea depends entirely on choriocapillary circulation, given the absence of retinal vessels; lack of oxygen would therefore lead to rapid loss of central or peripheral vision due to degeneration of neurosensory cells [6]. The Cuban team claim that improved photoreceptor metabolism, fostered by revitalization via a mechanism of angiogenesis, helps to keep vision cells actively functioning [6]. However, this explanation is refuted by Dr. Jean-Daniel Arbour, president of l'Association des médecins ophtalmologistes du Québec. He maintains that the scientific claims on which the treatment is based are incorrect; retinitis pigmentosa, a cellular disorder, *has nothing to do with blood circulation* [20].

Post-operative complications may occur. Cases of photophobia and strabismus with diplopia (double vision) are reported in the literature [6; 11; 12; 22]. Other possible complications include rupture or perforation of the scleral wall during the procedure [6]. There are also contraindications (e.g. active inflammation of the eye, vitreoretinal hemorrhage) [6].

The eye surgery is followed by ozone (O_3) therapy. According to the Cuban clinic's website, O_3 is administered rectally for 15 days (200 ml of a mixture of oxygen [O_2] and O_3, with a concentration of 50mg/l O_3 [6]. However, a summary of the Cuban study dating from 2004 refers to the O_3 being injected into the bloodstream. Blood is drawn from the patient, placed in a glass recipient containing heparin or sodium citrate, and brought into contact with a mixture of O_2 and O_3 at concentrations of 40µg/mL for 5-10 minutes; the blood is then re-injected into the patient [19]. Among the biological effects of the ozone, say the Cuban doctors, improving oxygen metabolism, cell energy and the antioxidant defense system may be beneficial for the retina in RP patients [8]. This ozone therapy is intended to boost the antioxidant defense system in order to minimize the damage caused by lipid peroxidation. The researchers base their claims on observations of subjects with age-related macular degeneration, who have high concentrations of lipofuscin pigments produced by lipid peroxidation. The hypothesis is that this may also apply to people with retinitis pigmentosa. However, *this assumption has not been borne out by fundamental research* and the Cuban researchers acknowledge that the ozone mechanism is not yet clear or fully understood theoretically [8].

The protocol also involves electric stimulation of certain parts of the head, neck, soles of the feet and palms of the hands. The idea is to produce a micro-massage of the blood capillaries and lymphatic system to promote electro-ionic balance. This treatment requires 10 to 15 sessions. To complete the protocol, drugs with various actions (hemorrheologic, oxido-reductive (lutein), immunomodulator or promoting lipid metabolism), multivitamins and minerals are administered [3; 6; 17].

3. Cuban study on impact of ozone therapy on RP

Because the RP treatment in Cuba is multimodal, Cuban researchers headed by Copello studied the impact of ozone alone on the visual field of subjects with RP [8]. Their findings were published in 2003 in *Ozone : Science & Engineering*, which is not a medical review but the journal of the International Ozone Association, which focuses on ozone technologies and technologies relating to oxidation.

The study was conducted between January 1999 and June 2000. The goal was to determine, prospectively, the efficacy of ozone therapy in patients with a typical form of RP (non-associated), by means of a randomized, controlled, double-blind study [8]. The sample consisted of 68 subjects: the 34 in the experimental (Ozone) group received 15 sessions of daily treatment with an ozone-oxygen mixture administered rectally via a catheter; for the other 34, the Control group, the protocol was identical except that oxygen alone was administered. Subjects could not undergo any other treatments at the outset or throughout the study (including vitamin supplements, vasodilators, magnet therapy and electric stimulation). The article does not specify whether or not the patients had undergone eye surgery prior to receiving the ozone treatments.

The Ozone and Control groups were comparable as regards various characteristics (age, gender, visual acuity, visual field, mode of inheritance of RP, stage of RP). The subjects' RP was staged according to a scale established by Peláez, director of the retinitis pigmentosa treatment centre in Havana. This classification comprises four

levels based on visual field; stage IV corresponds to the most advanced stage of the disease. Each group comprised nine people with each of the first three stages and seven with stage IV. The staging criteria are not described in the article by Copello, Eguía, Menéndez, & Menéndez (2003); they are only available in a book published in Cuba.

The main variable in the study was visual field area (VF), measured using the a Kinetic Goldmann perimeter. The area of the isopter, measured in mm^2, was defined by exploration with a V4 e white stimulus. A baseline measurement of the visual field was taken at the beginning of the protocol. Visual field was then measured monthly, 13 times in all. An improvement was considered to be significant if a VF increase of ≥ 25% was recorded and maintained for two consecutive months.

The results showed that overall, three times more subjects in the Ozone group experienced an improvement in their visual field than in the Control group (88.2% vs. 23.5%). The range of improvement deemed significant was almost three times greater than in the Control group (32.9% vs. 11.3% or 130.05 vs. 44.69 mm^2). *Note that this was an improvement recorded for two consecutive months and not necessarily maintained for the whole year.* In addition, a graph in the article by Copello et al. (2003) shows that this rate of 88% of subjects experiencing improvement was recorded in the 2^{nd} and 3^{rd} months post treatment, after which it declined steadily for the rest of the year. In other words, the effect of the ozone therapy was only temporary. Although during the first 5 months over 70% of subjects showed steady improvement in their visual field, at the 6^{th} month, this percentage dropped to around 55%. After the 7^{th} month, fewer than half of the subjects treated with ozone showed an improvement. At 10 months, the proportion was under 20%, and at 11 months, the likelihood of retaining the improvement was almost nil. Similarly the extent of the improvement also diminished (mean increase in visual field was 30.8% during the first six-month period vs. 18.9% in the second). Although this was not specifically analyzed during their study, Copello et al. concluded that half-yearly treatments (every 6 months) are necessary in order to conserve the improvement in visual field and slow down the expected deterioration.

The stage of the disease had a marked influence on how the Ozone group responded to treatment. Subjects with stage I and II RP were more likely to experience an improvement in their visual field than those with more advanced stages of the disease (64.7 vs. 29.4%). The mean improvement was also greater (47.7 vs. 21.8%). Note that the improvement in visual field in subjects at stages III and IV did not seem to be clinically significant because it was equivalent to the natural variation in visual field in RP patients, which according to Copello et al. is up to 20%.

The authors of this study acknowledge that it had certain limitations due to small sample size and the subjective nature of the variable measured, namely visual field [8]. In addition, the article does not present the findings concerning side effects of the treatment [8].

Other studies on the effect of ozone therapy (O_3 injected into the blood stream) have been conducted by Cuban researchers, but have only been the subject of brief abstracts of conferences on ozone [15; 16; 19]. Because these summaries provide

insufficient information, the results are not described here. On February 11, 2010, the author of the present document wrote to the Ozone Research Center in Cuba requesting further information about these studies but received no reply.

4. Cost of treatment

In 2009, the initial Cuban treatment of RP required three weeks' hospitalization and apparently cost just over $10,000 $ [20]. After this first phase, the patient has to return to the Centre every six months for an ozone treatment; according to the Cuban doctors, this is in order to maintain the improvement in their sight. In 2009, a six-monthly ozone treatment cost approximately $4,900 [20].

5. Criticisms of the Cuban protocol

The team headed by Dr. Peláez, who runs the retinitis pigmentosa treatment centre in Havana, began experimenting in the field of retinitis pigmentosa in the early 1990s. In 1997, in a comment published in the *Archives of Ophthalmology* reported by Garcia Liana [10], Dr. Peláez indicated that in view of the sceptical and antagonistic reaction to his research group, he had decided to postpone publishing his findings in a scientific review. He argued that publication of an article does not confer absolute scientific validity on a treatment. García Layana responded, in an editorial published in 2003 in *Archivos de la Sociedad espanola de Oftalmologia*, that in order to conclude whether or not a treatment is valid, it is important to publish at least the preliminary results when a new technique is used, so that other research centres can verify the validity of the results and in turn publish the results of their research [10]. Subsequently, if the treatment appears to benefit patients, a randomized, prospective, multicentre study is launched in order to obtain results based on scientific evidence [10].

Also in 1997, in another commentary, Dr. Peláez said he was planning to submit his results for publication to a periodical with a review committee [10]. The results of the study by Copello et al., members of the Peláez team, have since been published (2003), but in a specialized review devoted to ozone *(Ozone: Science & Engineering) not in a medical review*. However, critical *peer* review is important for the advancement of science and the launching of a dialogue with colleagues [7]. The manuscript submitted for publication is evaluated by a committee of individuals all competent in the field or fields of expertise touched upon in the article; this encourages authors to comply with the standards in their discipline and results in the publication of high quality material [7]. Evaluation is based on criteria relating to originality, quality of the science and impact on the scientific literature [7]. One of the goals of peer review is to prevent the dissemination of irrelevant results, unacceptable interpretations, personal or biased points of view . Because the Cuban approach is a *specialized medical* treatment, it was essential for the study results to be published in a *specialized medical* journal with a peer review committee of, for example, ophthalmologists or independent, impartial researchers specializing in the retina, in order to render the findings acceptable to the medical community. This did not happen.

Subsequently, García Layana (2003) expressed his surprise that in 6 years, the Cuban group had not yet published their results in a scientific (medical) publication with peer review [10]. The only findings to appear in a medical scientific review are those of Dr. Peláez, in a letter to the editor of *Archives of Ophthalmology* in 1997 [18]. García Layana points out that the results were purely subjective (visual acuity and visual field); no objective measure of deterioration was used, such as electroretinograms (ERGs), which is the objective proof usually presented of progression of RP, and which is reduced and becomes smaller as the condition worsens [2; 3; 10]. However, Layana does concede that visual field measurement can serve as a preliminary outcome even if it is subjective, because inter-study variability can be evaluated later. However, even in this respect, the results of other published studies, in which people operated on in Cuba were subsequently evaluated in Norway, Germany and the United States, did not demonstrate long-term improvement or stabilization of symptoms [3; 11; 12].

One of the independent studies assessing the impact of the Cuban procedure is that conducted by Berson, Remulla, Rosner, Sandberg & Weigel-DiFranco (1996). Ten persons were evaluated before being treated by the Cuban team and 6 to 8 months afterwards; the sample comprised 6 straightforward cases, 3 with X-linked recessive retinitis and 1 case of Usher syndrome type II. Following the treatments, all patients subjectively reported an initial improvement in some aspect of their vision, though two of them later said they were unsure whether their vision had improved. At the follow-up evaluation 6 to 8 months post surgery, overall, no significant changes in acuity or visual field were observed compared with the pre-surgery measurements. Moreover, after an outlier was removed from the database, the results showed that on average, *the visual field had diminished by 12.9%.* According to Berson et al. (1996), if this result is extrapolated over a one-year period, we obtain a steeper decline than would normally be expected with the natural progression of RP, which is around 4.6% to 15.5% [2; 3]. In addition, a significant mean reduction of 15.5% of the 30-Hz cone ERG amplitude was recorded. This decline, extrapolated over one year, is similar to or slightly greater than that observed in other one-year follow-up studies of RP patients, which is around 10% to 18.5% [2; 22]. Berson et al. also report that one of their patients displayed a definite improvement on the visual field and acuity tests after an initial intervention by the Cuban team, but after another procedure performed by the same team, the results were worse, even compared with the patient's condition prior to the first surgery. Accordingly, Berson et al. concluded that the Cuban treatment protocol does not result in any improvement in retinal function, despite subjective reports of improvement by patients. They even suggested that the procedures could, on average, aggravate the disease. In his book about ozone therapy, Bocci (2005) supports this conclusion [4]. García Layana (2003) is more cautious, noting that the sample in the study by Berson et al. comprised only 10 people, so we should not necessarily assume that the treatment is harmful [10]. His overall conclusion is that in the absence of external studies corroborating the Cuban findings, it is difficult to say whether or not the treatment is beneficial [10].

A Norwegian study investigating 8 patients (6 with RP and 2 with Usher syndrome) who had been treated in Cuba also failed to record any improvements in vision six months after the procedures [12].

Another critique of the Cuban protocol is that of ophthalmologist Dr. Heinrich Gerding. In a 1996 editorial, he wrote that Dr. Peláez persuaded his patients not to undergo an ERG examination during the 6 months following their treatment, claiming it could reverse the therapeutic effects [11]. As a result, hardly any of the German patients treated in Cuba underwent the post-treatment examination proposed by Dr. Gerding's team, which was extremely detrimental to his study. In addition, Gerding reported that two of his patients treated in Cuba developed severe restriction in extraocular movement, with diplopia. Corrective surgery was required. For this reason, in 1992, the German doctors asked Dr. Peláez for information about the procedure; he did not reply [11].

Using ozone for medical purposes is highly controversial. While some people agree that this gas possesses remarkable curative properties, others argue that this claim has no scientific basis and that the beneficial effects of O_3 remain scientifically unproven. In the last 20 years at least, Bocci (2005, 2006) has published a number of scientific works and articles on the therapeutic use of ozone. He reports that the gas can be beneficial in among other fields, dentistry, and for certain diseases (e.g. acute and chronic infectious diseases; autoimmune disorders; chronic ischemia; orthopedic disorders; certain types of chemotherapy-resistant metastatic cancer) [5]. The results achieved are above all due to the highly disinfectant properties of ozone and enhanced oxygenation, which fosters healing. However, Bocci remarks that *ozone therapy has failed in the case of RP because it is rarely and hardly beneficial for these patients*. He also points out that intravenous injection of ozone is not risk-free; it may cause pulmonary embolism and death or contain a toxic level of hypochlorous acid [5]. This is why some countries prohibit such injections. Another researcher, Baumgartner (2000), states that in RP, ozone treatments do not significantly increase tissue oxygenation [1]. In his view, all that the short-term improvements do is temporarily *mask* the vision deficits caused by RP; they have little or no effect in halting the progression of retinal cell death. On the contrary, says Baumgartner, they may accelerate it. Finally, an editorial review published in 2004 in the *International Journal of Artificial Organs* pointed out that many articles had been published on the medical use of ozone; however, knowledge in this field is incomplete because there are very few animal studies confirming the efficacy of ozone [9].

According to the Canadian Ophthalmological Society, the Cuban procedure "this procedure has not been subject to critical review and, as such, remains outside the medical mainstream. The Cuban clinic where it has bene performed has repeatedly refused to show the procedutre to anyone outside of the clinic.". [21]. The Society also points out that there have been reports of physical damage to some patients, including detached retinas, crossed eyes and sensitivity to light. Therefore the RP Research Foundation in Canada and the Foundation Fighting Blindness in the United States have questioned the validity of the method. And as mentioned, Dr. Jean-Daniel Arbour, president of l'Association des médecins ophtalmologistes du Québec, has stated that the scientific claims forming the basis for the eye surgery offered in Cuba are inaccurate, because retinitis pigmentosa is a cellular disease *unrelated to blood circulation* [20]. Also according to him, the efficacy of the Cuba treatments has never been proven by valid medical studies.

Finally, as mentioned, the surgery is not risk free; injuries to some patients have been reported and include detached retina, strabismus and light sensitivity [6; 11; 12; 22].

6. Conclusion

Many researchers and prominent organizations in the field of ophthalmology, including the Canadian Ophthalmological Society, the RP Research Foundation in Canada, the Foundation Fighting Blindness in the U.S. and l'Association des médecins ophtalmologistes du Québec, cast doubt on the validity of the Cuban treatments for retinitis pigmentosa, or regard them as useless. Among other arguments, they point out that the scientific claims upon which the proposed eye surgery is based are wrong, that there may be post-operative complications, and that the efficacy of these treatments has never been proven by valid medical studies. Even Bocci (2005, 2006), a renowned figure in the field of ozone therapy, does not recommend using ozone to treat retinitis pigmentosa. Moreover, the study published by the Cuban team found that ozone therapy only improves the visual field temporarily, and only in individuals in the early stages of the disease. Patients in more advanced stages rarely respond to the treatments and their condition shows little, if any, improvement. The Cuban researchers recommend six-monthly ozone treatments for people in the initial stages, but no longitudinal studies have been published on the effects of this therapy in the longer term or of repeating it at six-monthly intervals. The only principal variable in the one study published by Cuban researchers is visual field, which is subjective. No measurements were conducted using electroretinography to enable the progress of the disease to be observed objectively; this greatly weakens the validity of the results. Moreover, the results of this study were not published in a *medical* journal; they appeared in a publication devoted to ozone or oxidation-related technologies. However, *peer review* by independent, impartial experts, in this case ophthalmologists, is key for the advancement of science and scientific recognition.

No independent studies have demonstrated either an improvement or stabilization of symptoms in the long term following the Cuban treatment. Berson et al. (1996) even suggested that the procedures undergone by these patients in Cuba may, on average, have worsened the course of their RP.

Based on current knowledge, it is thus impossible to confirm that the Cuban treatment is valid or to recommend it. Promising therapies will only become available when we discover the exact mechanisms underlying the cellular dysfunction and know how to replace defective genes, block defective protein translation, or attenuate the biochemical pathway damage or abnormal function of the defective gene product [13; 22].

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