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Impact of Artrolife on hematological, reproductive, and thyroid function in female rats

W. S. A. H. Al-Khafaji*, D. A.-H. K. Al-Essawi**, N. M. H. Alshabi***

**University of Kerbala, Kerbala, Iraq*
***University of Kufa, Al-Najaf Al-Ashraf, Iraq*
****Al-Furat Al-Awsat Technical University, Karbala, Iraq*

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Department of Microbiology, College of Medicine, University of Kerbala, Kerbala, Iraq. E-mail: wafia.sh@uokerbala.edu.iq

Department of Biology, Faculty of Education for Women, University of Kufa, Al-Najaf Al-Ashraf, Iraq. E-mail: dalala.alesawi@uokufa.edu.iq

Department of Community Health, Technical Institute of Karbala, Al-Furat Al-Awsat Technical University, Karbala, Iraq. E-mail: noor.hussein.ikr35@atu.edu.iq

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Artrolife, a widely used nonsteroidal anti-inflammatory drug (NSAID), is commonly administered to alleviate pain, fever and inflammation. This study explored the influence of Artrolife on hematological, reproductive, and thyroid functions in female rats. Twenty adult female rats were randomly assigned to a control group receiving distilled water and to a treatment group administered Artrolife at 0.190 mg/kg body weight daily. After 7 and 20 days, blood samples were collected to assess hematological indices and hormone levels. The results revealed that Artrolife administration led to a noticeable increase in leukocyte count, alongside reductions in erythrocyte count, mean corpuscular volume and mean corpuscular hemoglobin. Furthermore, reproductive hormones such as FSH and LH experienced significant declines, while thyroid hormones displayed marked alterations; T_3 and T_4 levels increased, and TSH levels decreased notably after prolonged treatment. These findings indicate that Artrolife exerts substantial effects on both blood parameters and endocrine function, potentially disrupting normal physiological balance. The outcomes of this research point to the necessity for further investigations, particularly concerning the long-term implications of Artrolife use in clinical settings.

Keywords: anti-inflammatory effects; ovarian function; hormonal balance; hematological parameters; endocrine disruption; female reproductive health.

Introduction

The drug Artrolife belongs to the group of non-steroidal and anti-inflammatory drugs. These drugs reduce pain, fever and inflammation in the body by reducing the biological production of prostaglandins, which are mediators of the fever and pain in infections, so reduction in the levels of these chemical mediators by these drugs ultimately causes a reduction in inflammation pain and fever (Bosch et al., 2022). Artrolife was approved for the first time by the Food and Drug Administration in the United States of America in the year 1965 and this drug and other nonsteroidal anti-inflammatory drugs work primarily by inhibiting the enzymes known as cyclooxygenase which are responsible for the synthesis of prostaglandins, mediators of pain, fever and inflammation (Wongrakpanich et al., 2018). Research has indicated that Artrolife may have other mechanisms that help to perform its anti-inflammatory action but these mechanisms are not fully understood. The most important of these is its effect on inhibiting neutrophil activation and chemotaxis, decreasing the concentrations of inflammatory cytokines and altered lymphocyte activity (Oliver et al., 2021). This drug is useful in the treatment of various infections of the vertebrae, joints, tendons and endocarditis as well as gout and the treatment of various headaches (Sedeeq et al., 2017), diabetes insipidus and renal colic (Dayal et al., 2014). It is also used to treat retinal disorders and menstrual disorders in the women (Sedeeq et al., 2021). It is also used in treatment of mild and moderate states of COVID-19 (Fazio et al., 2023), as well as closure for patent ductus arteriosus in children (Kaya et al., 2023). Artrolife is also important in delaying premature birth by stopping labor in the early stages of pregnancy and thus prolonging it and this drug is useful for treating and reducing amniotic fluid infections around fetuses (D'Ambrosio et al., 2023). However, this may be accompanied by harmful and dangerous side effects affecting the mother or fetus during the various stages of pregnancy and some studies also showed that these drugs affected the fertility of male and female rats before pregnancy (Al-Essawia et al., 2020). The use of Artrolife is accompanied by many other negative effects, the most important of which is serious digestive disorders such as gastric ulcers and gastric bleeding, which can cause death to the patient as indicated by the US Food and Drug Administration. Artrolife may also lead to serious heart problems because non-steroidal anti-inflammatory drugs increase the incidence of heart attacks, stroke and heart failure and this risk increases when the drug is taken in high doses or for long periods against the background of pre-existing heart problems or risk factors that stimulate heart problems (Mohsein et al., 2023). This drug affects a number of other drugs while some drugs can in turn affect the effectiveness of this drug. For this reason every patient must tell the doctor about the drugs he takes whether without a prescription or with a prescription (Bouck et al., 2018). Artrolife should not be used during pregnancy, especially pregnancy at the stage of 29 weeks because it may cause heart disorders for the fetuses (Al-Essawi & AlJamali, 2019). This drug is absorbed by the digestive system, about 90% of it being absorbed within four hours and the maximum absorption of the drug is within two hours (Lateef et al., 2024).The half-life of this drug is not stable due to either the hepato-intestinal circulation, which is about 4–5 hours in its presence, while the half-life is 90 minutes in its absence (Ronchetti et al., 2017), or as a result of the proportion of the drug that binds to the plasma protein at high levels, as the proportion of the free drug increases when the drug binding sites are saturated with the plasma protein, stimulating its harmful effects and increasing the excretion of the drug outside the body in the urine and feces (Barkin, 2015).

Materials and methods

The total number of animals used in this study was 20 adult female rats of *Rattus rattus* with an average weight of 225 g and an average age of 11.5 weeks. The animals were brought from the Faculty of Science / University of Kufa and left in the animal house of the Faculty of Education for Girls for a certain period of time to be adapted before the start of the study experiment. These rats were placed in cages made of plastic with metal covers under the same laboratory con-

ditions conditions of humidity, lighting (12 hours light: 12 hours darkness), temperature (23–25 °C) and ventilation. The rats were given food and water ad libitum throughout the study period.

The drug Artrolife was in the form of capsules (Torge Medical Gmbh, Hamburg, Germany) with a concentration of 50 mg and from this the concentration used in the current experiment was prepared, which was about 0.190 mg/kg of body weight. The drug was dosed according to the weight of the rats.

One experiment was conducted for the purpose of detecting changes in various physiological and hormonal parameters of the blood of female rats caused by treatment with Artrolife. The rats were divided into 2 groups, each containing 10 animals: the rats in the first group received distilled water only and was the control group, while the second group was treated with Artrolife. The treatment of the study group animals continued for about 7 days and 20 days respectively, as 5 female rats from each group were dissected after 7 days while the other 5 rats in each group were dissected after 20 days of treatment. The rats in both groups were dosed daily in a single dose by an oral gastric dosing device.

After dosing for 7 days, the first group of rats (5 + 5) from each group was dissected, while the second group of animals (5 + 5) from the same groups was dissected on the 20th day of treatment. The female rats were dissected after they were anesthetized with diethyl ether, then the females were fixed in the dissection dish and 5 mL of blood was drawn with a sterile syringe from the heart directly by heart puncture method. 2 mL of blood drawn by tubes containing an anticoagulant substance (EDTA) was used to measure the following physiological parameters: total count of leukocytes, the number of erythrocytes and erythrocyte constant values (mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH)), while the rest of the blood 3 mL withdrawn was placed in gel tubes which did not contain anticoagulant substance. Following this, blood samples in gel tubes were left at laboratory temperature for 20–30 minutes to coagulate, after which the samples were centrifuged in a normal centrifuge for 30 minutes and 3000 cycle to separate the serum, which was collected and kept at a temperature of –20 °C to study the hormonal parameters which were represented by the female hormones (LH and FSH) and thyroid hormones (T_3 and T_4) and TSH (Boskabadi et al., 2013).

Physiological parameters in this study were assessed in scientific laboratories using the electronic complete blood test (CBC) device of the type (Sysmex). Levels of serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) and levels of thyroid gland hormones (T_3 and T_4) and thyroid-stimulating hormone (TSH) in the serum were measured using methods of enzyme-linked immunesorbet assay ELISA (BioTek Co., Ltd., USA).

The results of the current experiment were analyzed by means of (SPSS) system 21, the values of the studied parameters represented by mean ± standard error (x ± SE) which were extracted using F-test under the level of probability ($P < 0.05$) and the significant differences were found between groups treated using the least significant difference (LSD) according to Morgan et al. (2010).

Results

The study results showed statistically significant differences between the control group and the Artrolife treatment group after a 7-day treatment period (Table 1). A significant increase in the white blood cell count was observed in the Artrolife group (6.75 ± 0.12 × 10^3/mm³) compared to the control group (5.86 ± 0.37 × 10^3/mm³). In contrast, the red blood cell count recorded a significant decrease in the Artrolife group (3.60 ± 0.23 × 10^3/mm³) compared to the control group (4.87 ± 0.24 × 10^3/mm³). A significant decrease in the mean corpuscular volume (MCV) was also observed in the Artrolife group (63.1 ± 0.8 fL) compared to the control group (65.0 ± 0.0 fL). Similarly, mean corpuscular hemoglobin (MCH) content showed a significant decrease in the Artrolife group (20.0 ± 0.1 pg) compared to the control group (20.9 ± 0.2 pg). All these changes were statistically significant, indicating that Artrolife use significantly affected the studied hematological parameters.

Table 1
Comparison between the two study groups
in the physiological parameters for a 7-day treatment period

Parameter	Control group (G1)	Artrolife group (G2)
Leukocytes (×10^3/mm³)	5.86 ± 0.37	6.75 ± 0.12**
Erythrocytes (×10^3/mm³)	4.87 ± 0.24	3.60 ± 0.23*
MCV, fL	65.0 ± 0.0	63.1 ± 0.8*
MCH, pg	20.9 ± 0.2	20.0 ± 0.1***

Notes: * P < 0.05, ** P < 0.01, *** P < 0.001.

The results for the 20-day period showed significant differences between the control group (G1) and the Artrolife-treated group (G2) in several physiological parameters (Table 2). A significant increase in the number of leukocytes (5.81 ± 0.27 × 10^3/mm³ in G1 versus 7.95 ± 0.05 × 10^3/mm³ in G2) was observed in the treated group compared to the control group. The treated group also showed a significant decrease in red blood cell count (4.69 ± 0.24 × 10^3/mm³ in G1 versus 3.00 ± 0.23 × 10^3/mm³ in G2) and erythrocyte volume index (MCV 65.2 ± 0.3 in G1 versus 60.4 ± 0.1 in G2), as well as a decrease in corpuscular hemoglobin content (MCH 21.2 ± 0.1 in G1 versus 19.0 ± 0.2 in G2) in the treated group compared to the control group, with all these changes being significant.

Table 2
Comparison between the two study groups in the physiological parameters for a 20-days treatment period (mean ± SE)

Parameter	Control group (G1)	Artrolife group (G2)
Leukocytes, ×10^3/mm³	5.81 ± 0.27	7.95 ± 0.05**
Erythrocytes, ×10^3/mm³	4.69 ± 0.24	3.00 ± 0.23*
MCV, fL	65.2 ± 0.3	60.4 ± 0.1***
MCH, pg	21.2 ± 0.1	19.0 ± 0.2**

Notes: see Table 1.

The results for the 7-day period showed significant differences between the control group (G1) and the Artrolife-treated group (G2) in FSH and LH levels (Table 3). A significant decrease in FSH levels was observed in the treated group (1.75 ± 0.05 mIU/mL) compared to the control group (4.00 ± 0.01 mIU/mL). The results also showed a significant decrease in LH levels in the treated group (0.64 ± 0.62 mIU/mL) compared to the control group (1.56 ± 0.23 mIU/mL).

Table 3
Comparison between the two study groups
in the female hormones for a 7-day treatment period (mean ± SE)

Parameter	Control group (G1)	Artrolife group (G2)
FSH, mIU/mL	4.00 ± 0.01	1.75 ± 0.05***
LH, mIU/mL	1.56 ± 0.23	0.64 ± 0.62*

Notes: see Table 1.

The results for the 20-day period showed significant differences between the control group (G1) and the Artrolife-treated group (G2) in FSH and LH levels Table 4). A significant decrease in FSH levels was observed in the treated group (0.31 ± 0.15 mIU/mL) compared to the control group (4.36 ± 0.16 mIU/mL). The results also showed a significant decrease in LH levels in the treated group (0.35 ± 0.08 mIU/mL) compared to the control group (1.60 ± 0.24 mIU/mL).

Table 4
Comparison between the two study groups
in the female hormones for a 20-days treatment period (mean ± SE)

Parameter	Control group (G1)	Artrolife group (G2)
FSH, mIU/mL	4.36 ± 0.16	0.31 ± 0.15***
LH, mIU/mL	1.60 ± 0.24	0.35 ± 0.08***

Notes: see Table 1.

The results for a 7-day treatment period showed significant differences between the control group (G1) and the Artrolife-treated group (G2) in the levels of thyroid hormones T_3, T_4, and TSH (Table 5). A significant increase in T_3 levels was observed in the treated group (8.02 ± 0.02 ng/dL) compared to the control group (0.93 ± 0.10 ng/dL). A significant increase in T_4 levels was also observed in the treated

group (4.86 ± 0.01 µg/dL) compared to the control group (4.12 ± 0.05 µg/dL). In addition, there was a significant decrease in TSH level in the treated group (0.10 ± 0.05 µIU/mL) compared to the control group (0.14 ± 0.04 µIU/mL).

Table 5
Comparison between the two study groups in the physiological parameters for a 7-day treatment period (mean ± SE)

Parameter	Control group (G1)	Artrolife group (G2)
T_3, ng/dL	0.93 ± 0.10	8.02 ± 0.02***
T_4, µg/dL	4.12 ± 0.05	4.86 ± 0.01***
TSH, µIU/mL	0.14 ± 0.04	0.10 ± 0.05*

Notes: see Table 1.

The results for a 20-day treatment period showed significant differences between the control group (G1) and the Artrolife-treated group (G2) in the levels of thyroid hormones T_3, T_4, and TSH Table 6). A significant increase in T_3 levels was observed in the treated group (2.52 ± 0.15 ng/dL) compared to the control group (0.88 ± 0.12 ng/dL). A significant increase in T_4 levels was also observed in the treated group (6.30 ± 4.40 µg/dL) compared to the control group (4.16 ± 0.13 µg/dL). In addition, there was a significant increase in TSH level in the treated group (0.48 ± 0.43 µIU/mL) compared to the control group (0.13 ± 0.01 µIU/mL).

Table 6
Comparison between the two study groups in the physiological parameters for a 20-day treatment period (mean ± SE)

Parameter	Control group (G1)	Artrolife group (G2)
T_3, ng/dL	0.88 ± 0.12	2.52 ± 0.15***
T_4, µg/dL	4.16 ± 0.13	6.30 ± 4.40*
TSH, µIU/mL	0.13 ± 0.01	0.48 ± 0.43*

Notes: see Table 1.

Discussion

The results of this study recorded a significant increase in the total number of leukocytes, while a significant decrease in the number of erythrocytes and in some erythrocyte constant values (MCV and MCH) was observed in the blood of rats treated with Artrolife for 7 days and 20 days repectively when compared with control group for the same treatment periods. These results can be interpreted on the basis of the fact that the physiological parameters of the blood are one of the most important indicators of the toxicity of most of the non-steroidal anti-inflammatory drugs (NSAIDs) such as the drug used in this study. The increase in the number of leukocytes may be because this drug causes bleeding, which increases the number of leukocytes (Adedapo & Aiyelotan, 2001). Alternatively, this increase in the number of leukocytes may occur as a result of severe stress that leads to increase in fungal cells when this drug is taken (Zhao et al., 2020). When used for treatment, Artrolife stimulates damage to the tissues of the digestive system especially the stomach and duodenum, causing formation of perforations in addition to infections and inflammations, which lead to an increase in the total number of leukocytes, which increases with increase in the duration of treatment and the dose of the drug (Maqbool et al., 2006). Among the most important side – effect blood disorders of NSAIDs such as Artrolife is anemia known as aplastic anemia. This is considered a life-threatening disorder, and the anemia that accompanies the use of this drug occurs because this drug causes bleeding of the digestive system resulting from the inhibition of prostaglandins due to the ability of Artrolife to inhibit the action of COX enzymes, especially the enzyme COX 1, which perpetuates the mucous substance that protects the various parts of the digestive system. The inhibition of COX 1 leads to the occurrence of bleeding in the digestive system and this causes blood loss and the anemia (Farah et al., 2023), as shown in some studies which report that the rate of blood loss from the digestive system in patients taking some non-steroidal anti-inflammatory drugs is about 112 mL per day. This bleeding can be noticed by the red color of the stool when the drug is used for a short period while the color of the stool is black when the drug is taken for a long period of time (it may reach 4 months). However, bleeding or blood loss through the digestive system may be disguised or unnoticed and was estimated at 25 mL per day causing anemia as a result of a decrease in the number of red blood cells, which causes a decrease in hemoglobin levels in addition to a decrease in the values of other blood parameters such as MCV and MCH, which are related to the number of red blood cells and hemoglobin levels (de Jong et al., 2024). Some studies indicated that the low level of hemoglobin causes a lack of oxygen and stimulates the occurrence of cyanosis and blood acid in the respiratory system, which may lead to the death of animals within a short period (Farah et al., 2023; de Jong et al., 2024). One of the most harmful changes associated with the use of Artrolife is its effect on the digestive system, which is a major target for Artrolife and other steroidal anti-inflammatory drugs, which are rapidly and completely absorbed by this system (Mayo et al., 2016), stimulating common negative changes in the digestive tract such as perforations and ulcers causing hemorrhage and consequently anemia due to erythrocytopenia (Amir et al., 2023). Alternatively, the current results may be attributed to the occurrence of anemia, as some studies have shown that the active substance in the drug under study affects the hormone erythropoietin secreted from the kidneys and responsible for the generation of red blood cells from the bone marrow. This substance stimulates harmful effects in the kidneys (Abdulmuttaleb et al., 2024), causing low levels of the hormone erythropoietin, which stimulates decrease in the number of red blood cells and thus the occurrence of anemia in rats treated with the drug (Abdulmuttaleb et al., 2024). The results revealed a significant decrease in the levels of FSH and LH in serum of the group treated with Artrolife during the two periods 7, 20 days respectively when comparing the levels of these hormones in the serum of the control group during the same two dosage periods 7, 20 days respectively. These results can be related to the fact that prostaglandins are active fatty substances that are generated from the arachidonic fatty acid present in the cellular membranes for various parts of the body tissues. These chemical compounds are similar to hormones in their actions as they are chemical carriers but they differ from them in that they are not secreted from a specific glands but are produced directly by a chemical reaction at the site of injury of the body by means of cyclooxygenase, which are two types of enzyme cyclooxygenases (COX). The levels of prostaglandins' production increases when the body is harmed (Brown et al., 2023), though the prostaglandins' life peroid is short because the body breaks them down quickly and re-manufactures them to carry out their functions in the place of their formation, helping to restrict their actions and regulate their work. Prostaglandins exert various hormonal effects such as controlling ovarian cycle disorders as dysmenorrhea, ovulation and uterine contractions and stimulation the onset of labor in addition to playing an important role in the process of ovulation and other vital ovarian activities. Some studies have pointed to the prostaglandin receptors and prostaglandins synthase such as PGE and PGF, which carry out critical functional roles in the reproductive processes in females (Gaytán et al., 2006). Other studies have also indicated that prostaglandins are central neurotransmitters in the body affecting the hypothalamic-pituitary gland axis and thus these compounds are essential factors that control the release of hypothalamic hormones, which in turn affect the release of luteinizing hormone (LH) and stimulating hormone of follicles (FSH) from the pituitary gland. These activities are affected by changes that occur in the circulatory system such as the levels of reproductive stimulants. Therefore, since Artrolife and other steroidal anti-inflammatory drugs perform their work by inhibiting the biosynthesis of prostaglandins, which causes inhibition and disruption of the vital functions responsible for these compounds in various parts of the body and triggers various harmful side effects (Sohail et al., 2023), these drugs affect the prostaglandins that regulate the functions of the hypothalamus glands, which in turn affect the pituitary gland hormones, especially the hormones LH and FSH, causing a decrease in their levels as a result of the inhibition of prostaglandins in them (Athanasiou et al., 1996). Several hypotheses have been put to explain the actions of these compounds to liberate the hormones from the hypothalamus and thus control the release of pituitary hormones, as prostaglandins affect the membranes of these

glands, causing depolarization and an increase in the activity of calcium, which stimulates the secretion of the hormones (Gilman et al., 2021). Alternatively, these compounds may activate adenyl cyclase of the cell membrane, causing increased levels of cyclic AMP, which stimulates the secretion of hormones. It is believed that the system of prostaglandin receptors may be present in the pituitary gland perhaps as part of the mechanism of cyclic AMP, therefore the inhibition of the synthesis of prostagladins by Artrolife through inhibition the cycloxynenase enzymes responsible for the synthesis of these compounds (Maruyama et al., 2022). Some studies have indicated that Artrolife inhibits the synthesis of prostaglandins inhibiting the maturation of follicles and ovulation in rats by suppressing the hormones FSH or LH secreted by the pituitary gland due to its direct or indirect effect on the hypothalamus (Gilman et al., 2021). Carol & Ricard (1987) showed that the effects stimulated by Artrolife and other NSAIDs on the female reproductive system depend on various factors such as the age of the patient, the amount of the dose and the duration of intake of these drugs. Other studies found that Artrolife inhibited and delayed ovulation by directly affecting the quality of preovulatory follicles, which contain high levels of prostaglandins. Thus, this drug stimulates the inhibition of these compounds and delays ovulation (Wang et al., 2007). A study by Tsubo et al. (2009) has shown that this drug reduced female reproductive efficiency by suppressing the synthesis of ovarian prostaglandins, especially PGE2 and PGF2α, stimulating negative effects on female reproduction, such as preventing or delaying ovulation in females and inducing unruptured luteinzed follicle syndrome. The result of this study agreed with the results of (Pall et al., 2001). The results of this study indicated a non-significant increase in the levels of the thyroid hormones T_4 and T_3, while a non-significant decrease was found in the level of TSH after a period of 7 days, while the increase was significant in the levels of T_4 and T_3 hormones, and there was a significant decrease in levels of TSH hormone after a 20-day treatment period in the animals treated with Artrolife compared with the levels of these hormones after 7 and 20 days in the control group. The reasons for these results may be that non-steroidal anti-inflammatory drugs when taken orally affect functions and systems in different parts of the body, including hormone levels for most glands such as thyroid hormones (T_4, T_3), stimulating its rise by interfering with thyroid hormone sites with their carrier proteins in blood plasma, stimulating the lack of secretion of the hormone TSH. This leads to a decrease in its level in the plasma (Dobrzyn et al., 2020), as various drugs may affect the levels of hormones and thyroid functions through changes in the synthesis and metabolism and transport of thyroid hormones in addition to their effect on the biosynthesis of thyroid-stimulating hormone (TSH). Suppression of TSH in blood serum occurs as a result directly to unlock the associated T_3 and T_4 hormones, which is accompanied by a rise in levels of the free hormone (Bishnoi et al., 1994). Other studies recorded functional changes in the thyroid gland by studying the effect of this drug on iodine metabolism in the thyroid gland in rats treated with Artrolife or explain this result, as some studies have also shown that non-steroidal anti-inflammatory drugs (NSAIDs) change tests for thyroid function by removing the hormones T_4 and T_3 from plasma protein carriers because thyroid hormones are closely linked to protein. Thus the displacement causes an increase in concentrations of L_4 and free T_3 causing inhibition of TSH secretion (Bolton & Panciera, 2023).These results may also be explained by some studies showing that some commonly used non-steroidal anti-inflammatory drugs such as Artrolife have the ability to interact with the receptors of TSH hormone throughout the body, causing an increase in their levels in the plasma (Tal et al., 1988). Other research has also shown that patients who took NSAIDs showed negative effects of these drugs on the functions and levels of thyroid hormones, depending on the dose and the duration of treatment by these drugs. TSH remains the most optimal and important test for thyroid function because the level of this hormone is less affected by various measurement factors (41). The results of this study agreed with the results of (Nosivets et al., 2022).

Conclusion

It can be concluded that a steroidal anti-inflammatory drug causes abnormal changes in the studied blood parameters whether physiological or female hormones or thyroid hormones, causing a disturbance in their vital functions during treatment of 7, 20 days in rats. Therefore, we recommend studying the effect of NSAIDs on other hormones as well as increasing the duration of treatment with them to know their long-term effects.

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