Immunomodulatory efficacy of intravenous and oral chlorite solutions: a systematic review

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ABSTRACT

This article performs a systematic review of the available literature on chlorite anion (ClO_2^-) in clinical and preclinical trials, characterizing its efficacy to date as a clinical immunomodulatory treatment. The safety and efficacy of TCDO, WF10 and NP001, experimental drugs whose active ingredient is (ClO_2^-), as well as chlorine dioxide (ClO_2) solutions (CDS), a molecule that is metabolized to chloride and chlorite in the bloodstream, are therefore included. Chlorite, in its various formulations, has shown to be a complex immunomodulator; capable, at least, both of enhancing the immune response through phagocytosis or cellular defense mechanisms, and of mitigating the effects of the inflammatory response, inhibiting certain cytotoxic effects, as well as the hemolytic effects caused by free hemoglobin and the heme group. This intervention on the immune system response would be, in any case, the reason why chlorite has shown, in randomized controlled studies, to be effective in ailments as diverse as diabetic foot syndrome, AIDS, hemorrhagic cystitis or ALS. Some preclinical studies also point to a possible CDS antiviral effect. Maximum safe doses of 2.13 mg/kg/day of intravenous chlorite, and 2.9 mg/kg/day orally in the form of ClO_2 have been found. According to the available literature, there is sufficient preclinical and clinical evidence to conduct phase 2 and phase 3 clinical trials measuring the immunoregulatory potential of intravenous chlorite in certain pathologies. In the case of ALS, intravenous chlorite is ready to enter phase 3 trials or even marketing. Although there is a lack of clinical trials using chlorine dioxide, chlorite publications should be considered to study ClO_2, and vice versa.

KEYWORDS: Chlorite, WF10, NP001, chlorine dioxide, CDS, efficacy, immunomodulatory, anti-inflammatory, No-Observed-Adverse-Effect Level, NOAEL, Lowest-Observed-Adverse-Effect Level, LOAEL, ALS.

INTRODUCTION

Chlorite anion (ClO_2^-), the active principle of NP001 (an orphan sodium chlorite solution [1]), has recently gathered attention for its success in extending survival in ALS by 10.8 months for patients ≤ 65 years of age ($p < 0.05$) and by 14.4 months in patients aged ≤ 65 with high inflammation levels ($p = 0.002$) [2-4]. The attention received is justified by the fact that no other drug has achieved, through a double-blind clinical trial, such increases in the survival of ALS patients. However, this molecule could have a broader therapeutic potential, as it has been researched as a drug in animals and humans since 1972, with no review article to date that brings together all the studies published under its different drug designations (WF10, TCDO, NP001, CDS). There are review articles on CDS (Chlorine Dioxide Solution, whose active agent in the body is also the chlorite anion [5]), but only on its use as a mouthwash for different indications [6-8], on its toxicity thresholds (see below), and on its biocidal power on surfaces and environments. However, there is not a systematic review article on any therapeutic efficacy of intravenous chlorite, and we have only found one review article on chlorine dioxide solution (CDS) oral administration, limited to studies and cases published in Latin America to treat COVID-19 [9].

Therefore, this article examines, in the first place, chlorite as the active principle of the orphan drug NP001, investigated in ALS, and also found in the proprietary solution Tetrachlorodecaoxide (TCDO) or WF10, tested trough clinical and preclinical trials, intravenously and topically, for the anti-inflammatory treatment of difficult-to-heal wounds such as diabetic foot syndrome and post-radiation hemorrhagic cystitis (see tables). Its immunomodulatory effect has also been investigated in humans for advanced AIDS and the sequelae of oropharyngeal cancer (see tables). WF10 has also been found to improve glucose control in diabetes patients with severe foot ulcer syndrome [10] (**Fig. 1**). Chlorite's ability to regulate innate immune function has also recently been suggested as a potential treatment for Alzheimer's disease, Parkinson's disease and neuropsychiatric disorders such as depression [11].

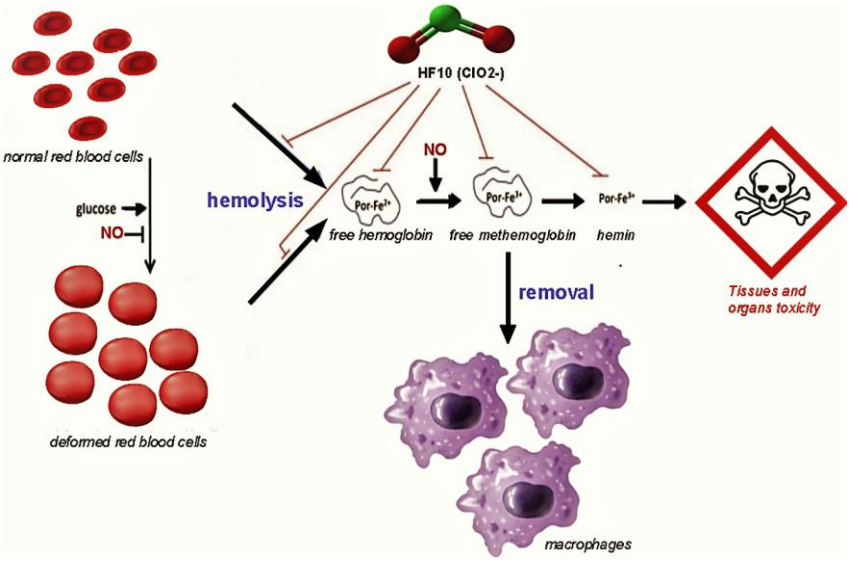

Figure 1. Proposed mechanism of action of WF10 in diabetes patients with severe foot syndrome. Red blood cells of diabetes patients are susceptible to hemolysis. Hemoglobin might be released from deformed cells (osmotically unstable). A hemolytic mechanism can also be mediated by hemin, which is highly toxic for tissues and organs. WF10 avoid hemolysis by inactivating hemoglobin and oxidized hemoglobin forms, inducing the removal of damaged red blood cells by macrophages [13].

Additionally, since Chlorine Dioxide (ClO_2) is absorbed in the gastrointestinal tract and reduced mostly to chlorite and chloride ions in the bloodstream [5, 12-16], and thus chlorite and ClO_2 are usually studied together in toxicological reports [17,18], this article collects the available studies that might be useful for ClO_2 use as a potential treatment. They were mainly conducted to evaluate ClO_2 safety and toxicity, and also as a potential therapeutic drug for some respiratory viruses such as PRRSV and IBV (see tables).

MATERIALS AND METHODS

Search strategy and selection criteria

Pubmed, SCOPUS, and Europe PMC databases were used for this article until December 26, 2024. These databases were searched for "chlorite", "WF10", "TCDO", "Tetrachlorodecaoxide", “Chlorine Dioxide” and "CDS", alone and in combination with the words "efficacy", "toxicity" and "safety". Further selection criteria were applied (**Fig. 2**).

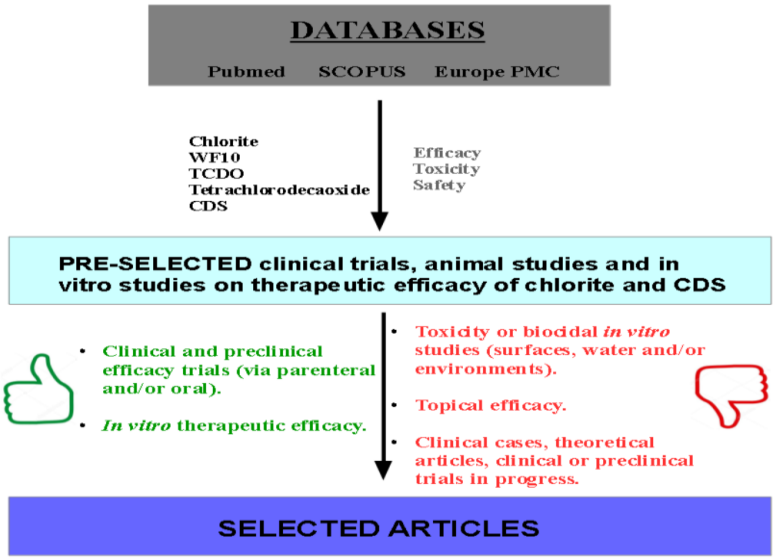

Figure 2. Search strategy and selection criteria for bibliography references. The Pubmed, SCOPUS, and Europe PMC databases were searched for "chlorite", "WF10", "TCDO", "Tetrachlorodecaoxide", “Chlorine Dioxide” and "CDS", alone and in combination with the words "efficacy", "toxicity" and "safety". The literature cited for clinical trials, animal studies and in vitro studies on the therapeutic efficacy of chlorite and Chlorine Dioxide (ClO2) was also reviewed. In selecting the articles, clinical and preclinical efficacy trials on any pathology published with parenteral and oral sodium chlorite, WF10, and ClO_2 were comprehensively included. *In vitro* studies aimed at the potential therapeutic efficacy of ClO_2, sodium chlorite, and WF10 in any disease were also included. *In vitro* studies on the toxicity or biocidal efficacy on surfaces, in water, and in environments of ClO_2 and sodium chlorite were excluded, except for a small sample. Animal toxicity results are not described, as there is sufficient evidence in humans and comprehensive reviews are available [19,20]. Studies on topical efficacy were excluded. Clinical cases, theoretical articles, as well as clinical or preclinical trials currently in progress, were excluded.

RESULTS

The available evidence on the potential therapeutic efficacy of NP001, TCDO/WF10 and CDS in cell culture and animal models will be presented below. Subsequently, results on efficacy and toxicity in clinical trials will be shown.

Efficacy in in-vitro studies

Chlorite was first investigated in the TCDO formulation (later called WF10), consisting of 4.25% chlorite ions, 1.9% chloride ions, 1.5% chlorate, and 0.7% sulfate ions together with sodium cations in aqueous solution. This drug was initially conceived for topical use, as an aid to wound and ulcer healing, repairing tissues based on studies advocating its power to stimulate macrophage migration and activation [19-21]. But studies soon began to show potential in its parenteral application. Specifically, for the ability to oxygenate tumor tissue so that it would become more sensitive to radiotherapy [22]. Simultaneously, their antibiotic potential was investigated in blood infected with 10 types of bacteria, showing an ability to temporarily stop their growth at 15 µg/ml, and sustainably decrease it to 150 µg/ml. This study also showed an increase in cell oxygenation, without appreciating that this oxygen was invested in cellular respiration, but rather that phagocytes increased their rate of phagocytosis [23]. Subsequently, the antiviral capacity against herpes and HIV was investigated, showing a direct reduction of free viral particles without exerting a strong cytotoxic effect [24,25].

Then, WF10 began to be researched for its immunomodulatory power, which is complex. Tissot et al. observed, *in vitro* and *in vivo*, that WF10 reduced leukocyte superoxide generation, inferring a possible anti-inflammatory effect [26]. McGrath et al. [27] proposed that it could down-regulate inappropriate immune activation of the organism by interfering with T-cell responses to antigens. Wabnitz and Samstag [28] would later concretize this mechanism, showing how WF10 prevents T cells from detaching from the first target cell, preventing them from producing serial cytocide. Marcinkiewicz et al. [29], Schempp et al. [30], and Giese et al. [31], for their part, observed that WF10 generates chloramine taurine (a cell-protective non-toxic oxidant), which inhibits adaptive immune responses while promoting the organism's endogenous defense mechanisms. Kühne et al. showed how WF10 increases the cytotoxic power of natural killer (NK) cells, promoting their adhesion to cancer cells such as leukemia and pancreatic cancer cells [32]. Pichert et al. [33] and Flemmig et al. [34], showed that WF10 chlorite does not target red blood cell hemoglobin, but free hemoglobin, transforming it to methemoglobin while destroying

methemoglobin and efficiently reducing ferric hemoglobin and hemin, two molecules that cause great tissue damage in severe inflammatory processes.

A search for "Chlorine Dioxide" returned 1782 results in the *Pubmed* database on February 20, 2025. The vast majority (1459) have been published increasingly since 2001, and almost all refer to the ClO_2 power to eliminate or inactivate all types of microorganisms in water or on surfaces: viruses, bacteria, fungi, protozoa, biofilms or spores. For example, with respect to viruses, this review has detected articles concerning the ClO_2 ability to inactivate 29 types of viruses, including echoviruses [35], enteroviruses [36], poliovirus [37], rotavirus [38], norovirus [39,40], calicivirus [40], influenza viruses [41] and coronavirus [42,43]. Most recent systematic reviews have been conducted aiming to clarify the involvement of ClO_2 in mouthwashes and as a disinfectant in surfaces and water supplies [44] and for mouthwashes [6]. A recent study has also shown the relatively high sporicidal effectiveness of using ClO_2 as an alternative biocidal agent to control infections of *Clostridioides difficile* etiology, the most common cause of acquired diseases in hospitalized patients [45]. However, far fewer studies report on the ClO_2 action against pathogenic microorganisms while at the same time accounting for how body cells react to the product in a potential therapeutic use. This review will focus precisely on these studies, since within the *in vitro* studies, they are the ones that can best inform on the possibility, or not, of a ClO_2 antimicrobial potential within the body.

In this regard, several relevant studies with cell cultures have appeared in recent years. One study showed a ClO_2 antiviral capacity in pig cells infected with PRRSV (porcine reproductive and respiratory syndrome virus). The study observed that ClO_2 inhibits virus replication, in addition to degrading its proteins and genome, without damaging the cell. The study also showed that ClO_2 reduced the release of inflammatory cytokines produced in response to viral infection [46]. Another study shows how ClO_2 inactivates 98.2% of microbes at concentrations as low as 5 to 20 ppm, while 93.7% of the animal cells used survived at 200 ppm" [47]. Published hypotheses for this possible selective power point to ClO_2 being a potent oxidizing agent capable of killing small organisms (bacteria and viruses, among others) in seconds, while it takes much longer and requires larger quantities to be able to damage human or animal cells, which are larger and therefore possess more antioxidants with which to defend themselves against the oxidative power of ClO_2 [48]. A more detailed explanation of this hypothesis, and its possible usefulness in the COVID-19 pandemic, can be found in another paper published in 2020 [49].

Regarding cancer, a study shows that ClO_2 inhibits the proliferation of MCF-7 and MDA-MB-231 breast cancer cells, as well as LoVo, HCT-116, and SW-480 colon cancer cells, possibly through ROS (Reactive Oxygen Species) production [50]. Another study reports that a Chlorine Dioxide Solution inhibited the replication of DMS114 Small-cell lung cancer (SCLC) cells, while being less toxic to healthy human umbilical vein endothelial cells (HUVEC) that worked as control cells [51].

Table 1a Efficacy in *in vitro* studies

Authors	Year	Product	Cell type	Tested effect	Most relevant results
Ullman and Kühne	1985	WF10/ TCDO (chlorite)	Granulocytes and whole blood	Antibiotic Immuno-modulatory	Destruction of *E. Coli* bacteria and others at 150 μg/ml, and growth detention for two hours at 15 μg/ml. Phagocytosis stimulation.
Mueller-Klieser et al.	1987	WF10/ TCDO (chlorite)	Human and rodent haemoglobin	Tumor tissue oxygenation to sensitize them to radiotherapy	Dose-dependent O_2 release at 5, 10 and 15 μl of TCDO in haemoglobin concentrations of 3 and 6 g/l.
Tissot et al.	1990	WF10/ TCDO (chlorite)	Rats, PMN leukocytes, pleural exudate *ex vivo*	Anti-inflammatory	Reduction of PMN leukocytes superoxide generation at 300 μg of (p<0.001), 30 (p<0.05) and 3 μg (p<0.05) of TCDO. Reduction of 6-keto-$PGE_{1\alpha}$ and PGE_2 prostaglandins in pleural exudate at 1.5 and 0.3 (p<0.001), 0.1, 0.03 y 0.01 μmol (p<0.05) of TCDO. Dose-dependent inhibition of LTB4 leukotrienes generation in stimulated PMN leukocytes at 150, 300 y 1500 μM of TCDO (p<0.01). [Results tested simultaneously *in vivo* in rats, see table 3]
Dargan and Subak-Sharpe	1991	WF10/ TCDO (chlorite) catalyzed with bovine hemo-globin (400 $\mu g/ml^{-1}$).	Rodent BHK 21.	Antiviral against HSV-1 (Herpes simplex), HSV-2, REO-3, Gripe A, FLV, Ad-5, Polio-1, SFV y GV.	Toxicity: 80% cell viability with 0.1% of TCDO; 99% cell viability with 0.05% of TCDO. Reduction of infectivity by exposition to 24h of 0.1% TCDO (equivalent to standard treatment): 400000 times for HSV-1, 250000 times for GV, 3000 times for SFV, 500 times for avian flu. Dose-dependent reduction of HSV-1 virions.
Ennen et al.	1993	WF10/ TCDO (chlorite)	Human PBMC cells, U937 cell lines, T Molt-4 clone 8 lymphoma, ACH2.	Antiviral against HIV	Total HIV infectivity elimination with 155 μmol/l of TCDO during 1h, and 95% with 52 μmol/l. Dose-dependent reduction of the link ability of HIV gp120 glycoprotein, with 1.9, 5.7, 17 and 52 μM of TCDO. Coadjutant effect of 17 μmol/l of TCDO in the blocking of HIV late replication effect exerted by zidovudine.

Marcinkie-wicz et al.	1995	WF10/ TCDO (chlorite)	PBMC cells, monocytes	Immuno-modulatory, Anti-inflammatory	Generation of endogenous oxidative compounds like taurine chloramine, with immune-modulatory effects. Proliferation and IL-2 production of anti-CD3 stimulated PBMC were inhibited. In PBMC and monocytes, however, WF10 induced pro-inflammatory cytokines like IL-1beta, IL-8, and TNF-alpha. In the monocytic cell line THP-1, the activation of the transcription factors AP-1 and NFkappaB by WF10 was demonstrated.

Table 1b Efficacy in *in vitro* studies (continuation)

Authors	Year	Product	Cell type	Tested effect	Most relevant results
McGrath et al.	1998	WF10/ TCDO (chlorite)	T Lymphocytes, monocytes, dendritic cells (all human)	Immuno-modulatory	No toxicity was found with any of the tested concentrations. Dose-dependent inhibition of the antigen response to a variety of T lymphocytes, with TCDO concentrations between 1:200 and 1:800.
Schempp	2001	WF10/ TCDO (chlorite)	Human hemin, haemoglobin. Multiple proteins, amino acids and enzymes.	Anti-inflammatory immuno-modulatory	WF10 downregulates inappropriate inflammatory reactions through the transformation of amino residues into chloramines, especially taurine chloramine. Taurine chloramine inhibits the generation of macrophage inflammatory mediators.
Giese et al.	2004	WF10/ TCDO (chlorite)	PMBC and human monocytes	Immuno-modulatory	No toxicity with the doses used (200 μM of chlorite). Downregulation of the immune response of several T cells previously activated in PMBC cultures with PMA/ionomycin (p<0.001). Inhibition of the IL-2 segregation in cultures stimulated with PMA/ionomycin and antibodies anti-CD3. Exponential, dose-dependent formation of taurine chloramine (cell protector, inflammatory macrophage regulator) in the PMBC cells.
Kühne et al.	2011	WF10/ TCDO (chlorite)	Human	Immuno-modulatory against leukemia and pancreatic cancer cells.	Time-dependent stimulation of the cytotoxic power of natural killer cells (NK) against leukemia and pancreatic cancer cells (p<0.05).
Noszticzius et al.	2013	Chlorine Dioxide	Pig bladder	Antiviral	Chlorine dioxide is a size selective antimicrobial agent which can kill micron sized organisms rapidly but cannot make real harm to much larger organisms like animals or humans as it is not able to penetrate deeply into their living tissues. The circulation of multicellular organisms can provide an additional protection to these organisms against ClO2.

Pichert and Arnhold	2015	WF10/ TCDO (chlorite)	Human	Interaction with haemoglobin, methaemo-globin And ferritic hemoglobin	Determination of chlorite as the active principle of WF10/TCDO. Reduction of the cytotoxic species of haemoglobin that appear in pathologic situations of haemolysis. Conversion of the ferritic haemoglobin to methaemoglobin at a 114 M M^{-1} s^{-1} rate or 6600 M^{-1} s^{-1} rate, depending on its precedence. Inactivation of the methaemoglobin at a 8.3 M^{-1} s^{-1} rate. Conversion of oxyhaemoglobin to methaemoglobin at a 35.4 M^{-1} s^{-1} rate.

Table 1c Efficacy in *in vitro* studies (continuation)

Authors	**Year**	**Product**	**Cell type**	**Tested effect**	**Most relevant results**
Flemmig	2016	WF10/TCDO (chlorite) and variants	Human erythrocytes and plasma with heme	Anti-inflammatory, inhibitor of hemolysis caused by heme	Dose-dependent reduction of hemolysis caused by 100 μM of heme in erythrocytes (4 x 10^7 cells/ml), starting with a concentration of 6.3 μM of TCDO ($p \leq 0.01$). Reduction of hemolysis close to a basal level from 15.7 μM of TCDO ($p \leq 0.0001$). A chlorite mol inactivates about 2 moles of heme if there is direct interaction. 50.3 μM of TCDO destroys almost all the free iron and other subproducts of heme. Possible usefulness in severe inflammatory illnesses such as acute respiratory syndromes, sepsis, or severe burns, in which levels of hemopexin in plasma get greatly reduced.
Wabnitz et al.	2016	WF-10	cytotoxic T lymphocytes (CTLs)	Immuno-modulatory	Inhibition of cytotoxic T lymphocytes serial killing of target cells by inhibiting the attachment to second target cells, accompanied by LFA-1, F-actin and phospho-L-plastin enrichment. Synergistic inhibition of T-cell cytotoxic activity with calcineurin inhibitors FK506 and CsA.
Zhu et al.	2019	Chlorine dioxide	Porcine	Antiviral against Porcine reproductive and respiratory syndrome virus (PRRSV). Anti-inflammatory.	No toxicity with CLO_2 concentrations below 60 μg/ml. Dose-dependent inhibition of the PRRSV replication with 24 μg/ml ($p<0.01$), 30 μg/ml ($p<0.01$), and 36 μg/ml ($p<0.001$) of ClO_2. Dose-dependent blocking of the link between PRRSV and cells with 24 μg/ml ($p<0.05$), 30 μg/ml ($p<0.01$), and 36 μg/ml ($p<0.01$) of ClO_2. Complete inactivation of extracellular PRRSV virions in cultures with Marc-145 cells with CLO_2 concentrations of 24, 30, and 36 μg/ml. Reduction of inflammatory cytokines IL-6, TNF-α, and IFN-β with 24 μg/ml ($p<0.01$), 30 μg/ml ($p<0.01$), and 36 μg/ml ($p<0.05$) of ClO_2.

Yidiz et al.	2022	Chlorine dioxide	DMS114 small-cell lung cancer (SCLC) cells and human umbilical vein endothelial cells (HUVEC)	Anticancer activity	Chlorine dioxide significantly inhibited the proliferation of SCLC cells ($p < 0.01$) with less toxicity in HUVEC cells. Chlorine dioxide induced apoptotic cell death in SCLC cells through nuclear blebbing and vacuolar formation. Chlorine dioxide treatment did not induce cell cycle arrest in both cell lines.

Efficacy in animal studies

Animal studies with intravenous chlorite are listed in Table 3. Among the most relevant is the administration of WF10/TCDO or placebo to 60 mice 1h after intravenous infection of mice with Candida albicans. The treatment group showed a stimulation of the spleen DPFC lymphocytes ($p<0.01$), inhibition of the immune reaction with doses of 18.6 μmol/kg, and the determination of an optimal dose for survival increase: 6.2 μmol/kg/day. In experimental infections with the strictly anaerobic Peptostreptococcus intermedius, TCDO ameliorated the course of the infection not only at a dose of 3.1 μmol/kg b.w. but also at a higher dose of 12.4 μmol/kg, suggesting that chlorite might work better against anaerobic pathogens [52].

Besides, the administration of WF10/TCDO to mice exposed to X-rays was shown to be a potent stimulator of hematopoietic cells in the spleen [53]. It was also tested in rats exposed to X-rays in the colon, showing improvement in the mortality rate and mucosa [54]. In another similar study, a reduction in short-term mortality and a lower incidence of subsequent occurrence of various types of cancer, especially leukemia ($P<0.001$) and malignant epithelial tumors ($P<0.05$), were found [55].

Following the immunosuppressive hypothesis of previous in vitro studies [26-31], a series of *in vivo* studies were conducted by the beginning of XXI century, trying WF10/TCDO as a better tool for survival increase in heart transplants, since most regular immunosuppressors are life-long dangerous. Following a preliminary study in which WF10 increased survival of animals but did not prevent the transplant rejection [56], a second study was conducted in 2001, for hamster-to-rat heart transplants with high doses of WF10. No significative cardiac damage from WF10 was detected, and the survival of transplant recipients increased slightly in a dose-dependent manner [57]. Ultimately, a third study was conducted in 2002, showing a dose-dependent survival increase comparing WF10 with

placebo. However, WF10 did not improve transplant survival when compared to other regular immunosuppressants [58].

Regarding CDS, we have found only one peer-reviewed study addressing the CDS therapeutic efficacy in animal studies. In it, a significant increase ($P<0.01$) in longevity was observed in a group of bees drinking water containing 10 ppm (parts per million) and 100 ppm of CDS versus those drinking water containing 0, 1, 1,000, and 10,000 ppm [59].

Exceptionally, we have also selected an interesting study only available in preprint. In this work, CDS efficacy was studied in 30 chicken embryos inoculated with an avian coronavirus. As a result, the mortality of embryos treated with CDS was significantly reduced with respect to those of the control group ($p=0.004$); treated embryos had higher body mass growth ($p=0.017$), lower viral load ($p=0.03$), and lower incidence of epidermal congestion ($p=0.04$), hemorrhage ($p=0.002$), curling ($p=0.017$) and membrane thickening ($p=0.003$) [60].

Table 2a Efficacy in animal models

Authors	Year	Product	Dose, route	Illness/ intervention	N, animal model	Most relevant results
Lackett et al.	1972	CLO_2	(concentr.) 0, 1, 10, 100, 1000, 10000 ppm, orally	None	5000 (approx.) healthy bees.	Significant increase in the longevity of the honeybees that drank water with 10 and 100 ppm of ClO_2, compared to the others ($p<0.01$).
Gillissen et al.	1986	WF10/ TCDO (chlorite)	3.1, 6.2, 9.3, 12.4, 18.6 μmol/kg for 1-4 days, intraperitoneal route.	Candida Albicans	60 mice infected with Candida or control.	Stimulation of the spleen DPFC lymphocytes with repeated doses of 3.1 μmol/kg of TCDO ($p<0.01$). Inhibition of the immune reaction with doses of 18.6 μmol/kg of TCDO ($p<0.01$). Optimal dose for survival increase: 6.2 μmol/kg/day of TCDO.
Tissot et al.	1990	WF10/ TCDO (chlorite)	0.5, 1.5, 15 μmol, intrapleural route.	Pleural inflammation	Male rats with induced pleurisy.	Reduction of the exudative cells with 15 μmol of TCDO ($p<0.001$). Reduction of the superoxide generation in stimulated PMN leukocytes, with doses of 1.5 μmol of TCDO ($p<0.001$).
Sassy et al.	1991	WF10/ TCDO (chlorite)	0.8 ml.	Cancer after-effects from radiotherapy	Rats with X-ray damage in the colon.	Increase of the survival rate. Demonstrable signs of improved healing in the mucosa.

Mason et al.	1993	WF10/ TCDO (chlorite)	1 ml/kg/day for 5 days, intravenous route.	Radiotherapy after-effects.	384 mice exposed to X-ray or control.	Reduction of the radiation lethality rate ($p \leq 0.0003$). Spleen weight increase ($p<0.05$). Increase of the spleen and bone narrow nucleated cells ($p<0.05$). Formation of endogenous cell colonies in the spleen ($p<0.05$).
Kempf et al.	1994	WF10/ TCDO (chlorite)	0.5-1.0 ml/kg/day for 5 days, intravenous route.	Cancerous after-effects of radiotherapy.	221 rats exposed to X-ray or control.	Prevention of radiation-induced leukemia ($p<0.001$) and malignant epithelial tumors ($p<0.05$). Reduction of short-term mortality.

Table 2b Efficacy in animal models (continuation)

Authors	**Year**	**Product**	**Dose, route**	**Illness/ intervention**	**N, animal model**	**Most relevant results**
Hansen et al.	2001	WF10/ TCDO (chlorite)	0.5 ml in two doses (dilution of 1+5 and 1+1 with 0.9% NaCl), intraperitoneal route.	Heart transplant viability.	10 hamsters and 22 rats.	No signs of cardiotoxicity were found in WF10 for hamsters. Prolongation of cardiac xenograft survival. WF10 did not induce tolerance or inhibition of pathological signs of acute rejection.
Kemp et al.	2002	WF10/ TCDO (chlorite)	0.5 ml in two doses (dilution of 1+4 and 1+1 with 0.9% NaCl), intraperitoneal route.	Heart transplant viability.	42 subjects (hamsters and rats)	Immunosuppressant effect: reduction of the CD4 and CD8 T-cells ($p<0.05$). Dose-dependent survival increase compared to placebo. WF10 did not improve survival when compared to other immunosuppressants.
Zambrano -Estrada et al.	2020	ClO_2	0, 0,35, 3,5 mg/kg/day, parenteral route.	Avian infectious bronchitis coronavirus	30 chicken embryos	Mortality reduction ($p=0.004$). Decrease in the incidence of bleeding ($p=0.002$), thickened membranes ($p=0.003$), curling ($p=0.017$) and epidermal congestion ($p=0.04$). Increase the body mass growth ($p=0.017$). Decrease of the viral load ($p=0.03$).

Efficacy in clinical trials

WF10 or TCDO, administered intravenously at 0.5 ml/kg/day (2.13 mg/kg/day of chlorite) demonstrated, in a double-blind trial, sustained cytokine regulation in AIDS patients, achieving a statistically significant improvement

in immunological variables such as leukocytes (P=0.037), lymphocytes (P=0.027), CD19 molecules (P=0.045) or CD35 molecules (P=0.030). Consequently, none of the ten treated patients was hospitalized during the three months of treatment, compared to five of nine in the control group, who did require hospitalization (P= 0.01), while only one of the treated patients died after nine months of follow-up, compared to six in the control group (P= 0.02) [61].

In another randomized study of 102 patients, WF10 at 0.5 ml/kg/day intravenously showed a "significant reduction" in late hemorrhagic cystitis caused by radiotherapy versus cervical cancer in the treated patients versus those in the control group [62]. Patients in the treatment group showed less need for antibiotics (P=0.002) and antispasmodics (P<0.001), as well as a greater decrease in blood in the urine (P=0.01), which was also faster than in the control group (P=0.004). In a previous observational study, without a control group, 20 patients with the same complication received the same dose of WF10, showing, after two cycles of treatment, a total (45% of cases) or partial (35% of cases) recovery of late hemorrhagic cystitis. A follow-up was carried out 9 months later, and 65% of the cases had no recurrence of hemorrhage [63]. Based on these studies, WF10 was recommended as a treatment for radiation cystitis in a review article in *Nature reviews* [64].

Along the same lines, another study with 13 patients treated with intravenous WF10 significantly reduced mucositis (P=0.048) and dysphagia (P=0.009) caused by radiotherapy and chemotherapy treatment for oropharyngeal cancer [65].

Intravenous administration of 0.3 ml/kg/day of WF-10 was also shown to be useful for the treatment of diabetic foot ulcer in another randomized double-blind study of 40 patients [66]. The drug showed a significant reduction in wound severity (P<0.05), infection and inflammation (P<0.01), necrotic tissue (P<0.01), along with an increase in granular tissue (P<0.05).

Although this review does not include studies of topical application, it is worth noting a randomized double-blind study published in *The Lancet*, in which WF10/WF10 was tested in 271 patients for the healing of difficult wounds, showing significantly more effectiveness than 0.9% saline used as a control (p<0.001), especially for chronic venous ulcers and postoperative wounds [67]. It is also worth noting the existence of a published double-blind clinical trial with WF10 as a mouthwash for the treatment of chemotherapy-induced oral mucositis [68].

Regarding the use of NP001, three successive clinical trials (Phase 1, 2a and 2b) conducted in several US hospitals were published for the treatment of ALS with intravenous sodium chlorite. In the placebo-controlled Phase I trial, with a sample of 32 patients, no adverse effects were seen at a single dose of up to 3.2 mg/kg chlorite, and a dose-dependent decrease in systemic inflammation markers HLA-DR (P=0.0058), and inflammatory CD16 monocytes (P=0085) was found [69].

The phase 2A trial, published in the *Neurology* neuroinflammation section, observed that degenerative disease halted its progression in a subgroup of patients with increased levels of neuroinflammation. In this study of 136 patients, intravenous chlorite doses of 1 mg and 2 mg/kg/day were administered. 25% of patients receiving the high dose stopped disease progression during the 6 months of treatment, compared to 19% receiving the 1mg/kg/day dose, and 11% in the control group, which received a placebo [70]. Considering the historical matched controls available for 113 patients, the study points to improved statistical evidence of $p = 0.02$, which in itself is significant. However, that *p*-value is found by comparing only the highest dose with placebo. If the intermediate dose is also taken into account, as it should be, and the linear trend is analyzed by logistic regression, a $p = 0.004$ is found.

Although another phase 2B trial initially showed no significant differences between placebo and patients treated with NP001 at the measured endpoints, the treatment showed to be safe and well tolerated at 2 mg/kg/day. However, *post hoc* analysis identified treated individuals of ages 40 to 65 with slower declines in ALS Functional Rating Scale score and Vital Capacity loss compared to the placebo. A greater number of non-progressors were NP001-treated compared with placebo ($p = 0.004$) [71].

Some more *post hoc* studies have recently been published based on the samples and data provided by these clinical trials with NP001 for ALS. One of them traced the survival of patients in the already mentioned Phase 2A and 2B trials altogether, suggesting that a 6 months' treatment course of 2/mg/kg/day NP001 resulted in a 4.8-month increase in overall ALS patient's survival ($p = 0.04$), and in a 10.8 month increase in ALS survival for patients under 65 years of age ($p < 0.05$) [2].

Another study, also based on samples taken in the phase 2 and 2b studies with NP001 for ALS, shows how patients aged 40-65 years old with plasma CRP $\geq$ 1.13 mg/L (high levels of inflammation, measured by C-Reactive Protein activation) who were treated with NP001 maintained a better physical function (measured by ALSFRS-R score) than those in the control group ($p = 0.03$). Additionally, the study shows that biomarkers related to microbial

translocation were significantly decreased, compared to baseline values, in NP001-treated patients compared to controls, while wound healing and immunoregulatory factors were increased at the end of the study [72].

A third study, again based on samples taken in Phase 2a and 2b studies with NP001 for ALS, analyzed how patients ≤ 65 years old treated with plasma CRP ≥ 1.13 mg/L showed a 64% slower rate of respiratory vital capacity decline compared with placebo (p = 0.002). Those with plasma CRP < 1.13 mg/L (low levels of inflammation) showed no response. To test whether NP001 affects the immune system function, the trial measured two factors related to immune system regulation, Serum Amyolid A (SAA) and TGFB1 levels. For the first one, the study found a positive linear relationship of the log transformed baseline plasma CRP and plasma Serum Amyloid A (SAA) in ALS patients age ≤ 65 years old and high plasma CRP at baseline (p = 0.004). Then, the study found a significant TGFB1 increase over the 6-month trial in NP001 treatment compared to placebo controls in participants aged ≤ 65 years old with high plasma CRP at baseline (p = 0.02). This report is, therefore, the first to link a biomarker confirmed regulation of the innate immune system with a therapeutic approach for controlling vital capacity loss in ALS patients [11].

A complementary study by the same authors showed that a 6 months' treatment course of NP001 in patients aged ≤ 65 with elevated CRP (n=155) resulted in a median of 14.4 months survival increase (p=0.002) and a 29% less VC loss (p=0.02). Additionally, the study discovered that studied patients with low creatinine were younger (p=0.003), had a more advanced ALS (p=0.008), and responded better to treatment (p=0.02). The article firmly hypothesizes, again based on the results and samples from the NP001 trials, that ALS is an immune disease. The rebalancing of the innate immune system by chlorite would explain why patients having an innate immune disfunction increased their survival by almost a year and a half after only 6 months of intermittent therapy with NP001 formula [3].

Eventually, regarding CDS, other than clinical trials in which ClO_2 has been used as a mouthwash on oral mucosa [6-8], we do not yet have a published peer-reviewed controlled study with CDS being used orally or parenterally, we have only found preprints [73], cases [74,75] and testimonies.

Table 3a Efficacy and toxicity in clinical trials

Authors	Year	Product	Doses, route, duration	Type of study	N	Illness	Efficacy	Toxicity
Lubbers et al.	1982	Chlorine dioxide, chlorite, chlorine, chlorate, chlora-mine	0.03 mg/kg/day oral, 84 days.	Toxicity phase I study, controlled, randomized	60	None. A group of adults with low levels of glucose-6-phosphate dehydrogena se.	N/A	No evidence of a toxic effect was found.
Lubbers et al.	1984	Chlorine dioxide, chlorite, chlorine, chlorate, chloramin e	Up to 0,34 mg/kg, oral, 1 day	Toxicity phase I study, controlled, randomized, double blind	60	None.	N/A	No evidence of a toxic effect was found.
Raffanti et al.	1998	WF10/ TCDO (chlorite)	2.13 mg/kg/day, intravenous . 4 cycles of 5 days every 3 weeks	Placebo-controlled, randomized, double blind	19	Advanced AIDS	No need of hospitalization (p=0.01). Lymphocytes regulation (p=0.027). CD35 molecules regulation (p=0.030).	WF10 was "well tolerated". No significant toxicity effect was found in the renal or hepatic function, hematocrit, hemoglobin, and plaquettes.
Veera-sarn et al.	2004	WF10/ TCDO (chlorite)	2.13 mg/kg/day, intravenous . 2 cycles of 5 days every 3 weeks	Controlled, randomized, open label.	102	Hemorrhagic cystitis induced by radiotherapy	Decrease in the use of antispasmodics (p=0.001) and antibiotics (p=0.002). Faster decrease of blood in the urine (p=0.004).	No "serious concern about security" was found. Transient methemoglobinem ia, without statistical significance (p=0.134).
Penpa-ttanagul et al.	2007	WF10/ TCDO (chlorite)	2.13 mg/kg/day, intravenous . 3 cycles of 5 days every 3 weeks	Controlled, randomized, open label.	13	Head and neck cancer.	Reduction of dysphagia (p=0.009) and mucositis (p=0.048).	Slight increase of hemoglobinemia and leucopenia, without statistical clarity

Yingsak-mongkol et al.	2011	WF10/ TCDO (chlorite)	2.13 mg/kg/day, intravenous . 1-3 cycles of 5 days every 3 weeks	Placebo-controlled, randomized, double blind	40	Diabetic foot ulcer	Reduction of the infection, inflammation, and necrosed tissue (p<0.01). Reduction of the wound severity, and increase of the granular tissue (p<0.05).	No evidence of a toxic effect was found.

Table 3b Efficacy and toxicity in clinical trials (continuation)

Authors	**Year**	**Product**	**Doses, route, duration**	**Type of study**	**N**	**Illness**	**Efficacy**	**Toxicity**
Miller et al.	2014	NP001 (sodium chlorite)	0.2 mg/kg 0.8 mg/kg 1.6 mg/kg 3.2 mg/kg 1 day.	Phase I, placebo-controlled.	32	Amyotrophic Lateral Sclerosis (ALS).	Dose-dependent inhibition of systemic inflammation biomarkers (HLA-DR) (p=0.0058) and of inflammatory monocytes CD16 (p=0085).	No evidence of a toxic effect was found, measured up to 8 days after treatment.
Miller et al.	2015	NP001 (sodium chlorite)	1 mg/kg/day 2 mg/kg/day 6 cycles of 5 days every 3 weeks	Phase II, placebo-controlled, randomized, double blind	136	Amyotrophic Lateral Sclerosis (ALS).	Dose-dependent detention ALS progress in a subgroup of 113 patients matched with historic controls (p=0.004).	Sodium chlorite was "generally safe and well tolerated", except for infusion site pain and dizziness.
Miller et al.	2022	NP001 (sodium chlorite)	2 mg/kg/day 20 infusions over 6 cycles: Cycle 1, 5 consecutive daily infusions. Cycles 2-6, 3 consecutive daily infusions.	Phase 2B, placebo-controlled, randomized, double blind	138	Amyotrophic Lateral Sclerosis (ALS).	Post hoc analysis identified a greater number of non-ALS progressors compared to placebo (p=0.004).	Sodium chlorite was "generally safe and well tolerated", except for infusion site burning sensation.
Zhang et al.	2022	NP001 (sodium chlorite)	2 mg/kg/day 6 months	*Post hoc* analysis of Miller et al. clinical trials	55	Amyotrophic Lateral Sclerosis (ALS).	Patients aged 40-65 with high CRP levels maintained better physical function (p=0.03). Biomarkers related to microbial translocation were significantly decreased, compared to baseline values, in	Sodium chlorite was "generally safe and well tolerated", except for infusion site pain and dizziness.

							NP001-treated patients (*p=0.04*), while wound healing and immunoregulatory factors were increased.	
McGrath et al.	2023	NP001 (sodium chlorite)	2 mg/kg/day 6 months	*Post hoc* analysis of Miller et al. phase 2A clinical trial.	61 31	Amyotrophic Lateral Sclerosis (ALS).	Patients ≤ 65 years old treated with plasma CRP ≥ 1.13 mg/L showed a 64% slower rate of respiratory vital capacity decline compared with placebo (*p=0.05*), a positive linear relationship of the log transformed baseline plasma CRP and plasma SAA (*p*=0,004, n=31), and an increase of TGFB1 levels (*p*=0.02, n=31).	Sodium chlorite was "generally safe and well tolerated", except for infusion site pain and dizziness.
Forrest et al.	2024	NP001 (sodium chlorite)	1 mg/kg/day 2 mg/kg/day 6 months	*Post hoc* analysis of Miller et al. clinical trials.	268	Amyotrophic Lateral Sclerosis (ALS).	A 6 months' treatment course of 2mg/kg/day NP001 resulted in a median of 4.8-month increase in overall ALS patient's survival (*p*=0.04), and in a 10.8 month increase in ALS survival for patients ≤ 65 years of age (HR =0.69 (95% CI: 0.50, 0.95, *p*<0.05).	Sodium chlorite was "generally safe and well tolerated", except for infusion site pain or burning sensation and dizziness.
McGrath et al.	2024	NP001 (sodium chlorite)	2 mg/kg/day 6 months	*Post hoc* analysis of Miller et al. clinical trials.	189 155	Amyotrophic Lateral Sclerosis (ALS).	A 6 months' treatment course of NP001 in patients aged ≤ 65 with elevated CRP (n=155) resulted in a median of 14.4 months survival increase (*p*=0.002) and a 29% less VC loss (*p*=0.02). Patients with low creatinine were younger (p=0.003), had a more advanced ALS (p=0.008), and responded better to treatment (p=0.02).	Sodium chlorite was "generally safe and well tolerated", except for infusion site pain or burning and dizziness.

Safety and toxicity

The US EPA [17] jointly evaluates the toxicity of CDS and chlorite, creating an equivalence based on their molecular weights, whereby 1 mg $NaClO_2$ is equivalent to 0.75 mg ClO_2. From 25 of these studies published through 2000, the EPA determined a NOAEL (No-Observed-Adverse-Effect Level) of 3 mg/kg/day and a LOAEL (Lowest-Observed-Adverse-Effect Level) of 5.7 mg/kg/day for CDS. These levels included a study in several generations of mice, during estrus, lactation, and parturition, i.e. sensitive populations. The Agency for Toxic Substances and Disease Registry (ATSDR) replicated these EPA toxicity levels in a subsequent report, lowering the NOAEL from 3 mg/kg/day to 2.9 mg/kg/day [18].

Table 3 summarizes the toxicity results of all human studies conducted to date with chlorite and CDS. By the oral route, human studies have found no adverse effects in individuals consuming low concentrations (0.04-0.34 mg/kg/day) of CDS or chlorite in experimental studies [76-79] or consuming drinking water disinfected with CDS [80,81].

The studies that have administered higher doses and concentrations have done so with parenteral chlorite solutions. The most relevant trial is the one conducted in 2014 and 2015 with NP001. Phase I evaluated its safety and tolerability of acute (24h) exposure. Single escalating doses of up to 3.2 mg/kg/day were administered to 32 patients. All doses of NP001 were generally safe and well tolerated, and there were no serious adverse events or variations in relevant clinical parameters [69].

Subsequently, other multicenter, randomized, double-blind, Phase 2 and 2B clinical trials were conducted with NP001. In these trials, 45 out of a total of 136 and 69 out of 138 ALS patients received 2 mg/kg/day of sodium chlorite as a single daily dose intravenously for 6 months intermittently [70, 71]. The concentrations at which sodium chlorite was administered intravenously were 5700 ppm (63 mM) [82]. The studies resulted in Class I evidence that sodium chlorite was "generally safe and well tolerated," except for a burning sensation or pain at the infusion site and transient dizziness [70,71]. These studies were based on previous experience with chlorite in the WF10 or TCDO formulation. No significant adverse effects were observed in any of the clinical trials conducted with WF10.

DISCUSSION

Intravenous chlorite, in its various formulations, has been shown to be an immunomodulatory complex, capable both of enhancing the immune response through phagocytosis or cellular defense mechanisms and of mitigating the effects of the inflammatory response, inhibiting certain cytotoxic effects as well as the hemolytic effects caused by free hemoglobin and by the heme group. Other studies have hypothesized more potential chlorite mechanisms that might ultimately interfere with the immune system, such as an improvement in glucose control, a decrease production of superoxide ions or an increased tissue oxygen tension [83].

This intervention on the immune system response would be, in any case, the reason why WF10 has shown, in randomized controlled studies, to be effective in ailments as diverse as diabetic foot syndrome, AIDS, hemorrhagic cystitis, or ALS. In the case of ALS, three randomized placebo-controlled trials have been published in 2014 and 2015 to test intravenous chlorite. The main outcome of those studies did not come up until 2024, when the gold standard to measure any ALS treatment (survival increase rate) was analyzed for the patients studied in the aforementioned trials. This *post hoc* analysis shows the power of chlorite to extend survival in ALS patients by 10.8 months in patients ≤ 65 years of age ($p < 0.05$) and by 14.4 months in patients aged ≤ 65 with high CRP levels ($p = 0.002$). The significance survival increases justify conducting Phase 3 clinical trials or even marketing for NP001, since no other drug has been even close to achieve such a survival increase through a double-blind clinical trial.

Regarding chlorine dioxide, hypotheses about its mechanism of action should take into account the much more abundant studies with sodium chlorite, since both chlorine dioxide and sodium chlorite are reduced to chlorite anion (ClO_2^-) in the bloodstream [5, 12-16]. Some articles reviewed here also suggest a possible selective antiviral effect of ClO_2, similar to the effect shown by the product in laboratory studies and in clinical trials for topical applications on wounds and oral mucosa. This selectivity would be based on the fact that CDS is capable of rapidly and effectively oxidizing small microorganisms such as viruses or bacteria, while it is much more complicated for it to penetrate cells due to their size and the greater presence of antioxidants in them. These statements are, however, still hypotheses based on *in vitro* experiments that need further research to be corroborated.

Concerning toxicity, safe doses of WF10 have been broadly defined in the clinical trials reported here, and are at a maximum of 0.5 ml/kg/day (2.13 mg/kg/day chlorite; 0.75 mg/kg/day chlorate; 0.95 mg/kg/day chloride; 0.35 mg/kg/day sulfate). No studies in humans at higher doses have been published, but it is plausible to assume that

significant adverse effects begin to be observed at higher doses, since the study by Raffanti et al. [61] mentions unpublished data in which up to 1.5 ml/kg was administered, noting that adverse effects were found at amounts greater than 0.5 ml/kg. The maximum doses for the Miller et al. [70,71] Phase 2 trials with NP001 were based on studies previously conducted with WF10, so they are similar (2.13 mg/kg/day of chlorite in WF10 vs. 2 mg/kg/day of chlorite in NP001). In addition, the frequency of administration in 3- to 5-day cycles separated by several weeks is similar to the frequency of administration used in the WF10 trials.

In the CDS case, the maximum oral intake doses at which no toxic effects have been observed (oral NOAEL dose) have been established at 3 mg/kg/day and, subsequently, at 2.9 mg/kg/day [17,18]. These doses are supported by 25 studies in mice, rats, monkeys, and, to a lesser extent, humans, reviewed by the EPA [17,18]. Subsequent studies have found no toxicity below this NOAEL [47,84]. In 2019 and 2020, the FDA issued two releases warning of the danger of uncontrolled self-medication with CDS and sodium chlorite but did not specify the doses at which toxic effects begin [85-86].

From the NOAEL, the EPA also calculated the oral reference dose (RfD), i.e., the likely safe dose for uninterrupted (daily, lifetime) oral CDS consumption in all classes of humans (including those groups potentially most sensitive to ClO_2). This RfD is calculated by applying to the experimental NOAEL value of 3 mg/kg/day an uncertainty factor of 100, resulting in a reference value of RfD = 0.03 mg/kg/day. This is an indicator that is useful for determining, mainly, the CDS doses to be used for drinking water potabilization. However, it is not effective as a reference value for the absence of toxicity when CDS is to be used therapeutically for short periods of time, as it happens in clinical trials. For the latter case, the NOAEL (3 mg/kg/day) is the appropriate figure to indicate the maximum CDS doses that are safe for treating humans [5].

CONCLUSION

Preliminary evidence of the immunomodulatory efficacy of intravenous chlorite in the form of WF10/TCDO has been found for several pathologies with inflammatory or autoimmune responses, based on results of both preclinical and double-blind, randomized, controlled clinical trials. In particular, three clinical trials and some *post hoc* studies with NP001 show important results against ALS, in terms of a significant improvement in

patient's survival and vital capacity, especially in those with higher levels of neuroinflammation (see tables). These results encourage the conduction of phase 3 studies of intravenous chlorite for ALS (or even a more direct marketing approval), as well as phase 1 studies in other neurodegenerative diseases with associated neuroinflammation, such as Alzheimer's or Parkinson's. Besides, significant results of intravenous chlorite have been found through both preclinical and randomized controlled trials in pathologies with an inflammatory or autoimmune response as different as AIDS, post-radiation hemorrhagic cystitis, diabetic foot ulcer, or oropharyngeal cancer (see tables). These results should encourage researchers to continue phase 2 and phase 3 trials of chlorite for these pathologies, while suggesting the possibility that the molecule may be effective in other pathologies not yet investigated.

No published clinical trials with ClO_2 have been found. However, pharmacokinetic studies show that CDS is absorbed from the digestive tract into the bloodstream, where it is metabolized into chlorate, chlorite, and chloride ions (the latter two components of WF10), suggesting that published studies with sodium chlorite solutions (TCDO/WF10, NP001) should be taken into account in the study of chlorine dioxide, and vice versa, as it already happens in the more abundant toxicity studies. With regard to CDS preclinical studies, some point to a possible antimicrobial efficacy (see tables). The chlorite research pathway has been more prolific and robust so far, showing a complex effect of chlorite on the immune system, inhibiting its inflammatory response while potentiating other cellular defense mechanisms. This situation might well be found in *in vitro* and *in vivo* studies with chlorine dioxide, and calls for more preclinical research on chlorine dioxide that take into account on previous studies with sodium chlorite.

Safe doses of chlorite solutions are well established by EPA and ATSDR on of 3 mg/kg/day of intravenous chlorite, and 2.9 mg/kg/day orally in the form of ClO_2, based on 25 on studies in animals and, to a lesser extent, in humans. Afterwards, concentrations of 1mg/kg/day and 2.13 mg/kg/day of intravenous chlorite in 6-month cycles of 3-5 days per month have been tested in 300 humans without relevant adverse effects, other than site infusion pain.

LIMITATIONS OF THE STUDY

To avoid bias, this article has not systematically reviewed preprints, although it has cited some of the most significant ones due to their increasing importance [87].

In the case of safety and toxicity, only articles that have been performed in humans have been systematically reviewed, since there are already sufficient reports and reviews based on publications with animals and cell cultures.

Numerous patient testimonials and some clinical cases using chlorite solutions have been detected. Despite being an interesting place to look for potential clues, they have been excluded because of their low probative value.

Chlorite anion is a molecule whose mechanisms of action are multiple and still in an incipient process of study, so that no exhaustive or definitive delimitation of these mechanisms is offered in this article.

FUNDING

The authors received no funding for this research.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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