Enclomiphene Citrate

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEETING

JUNE 8TH, 2022

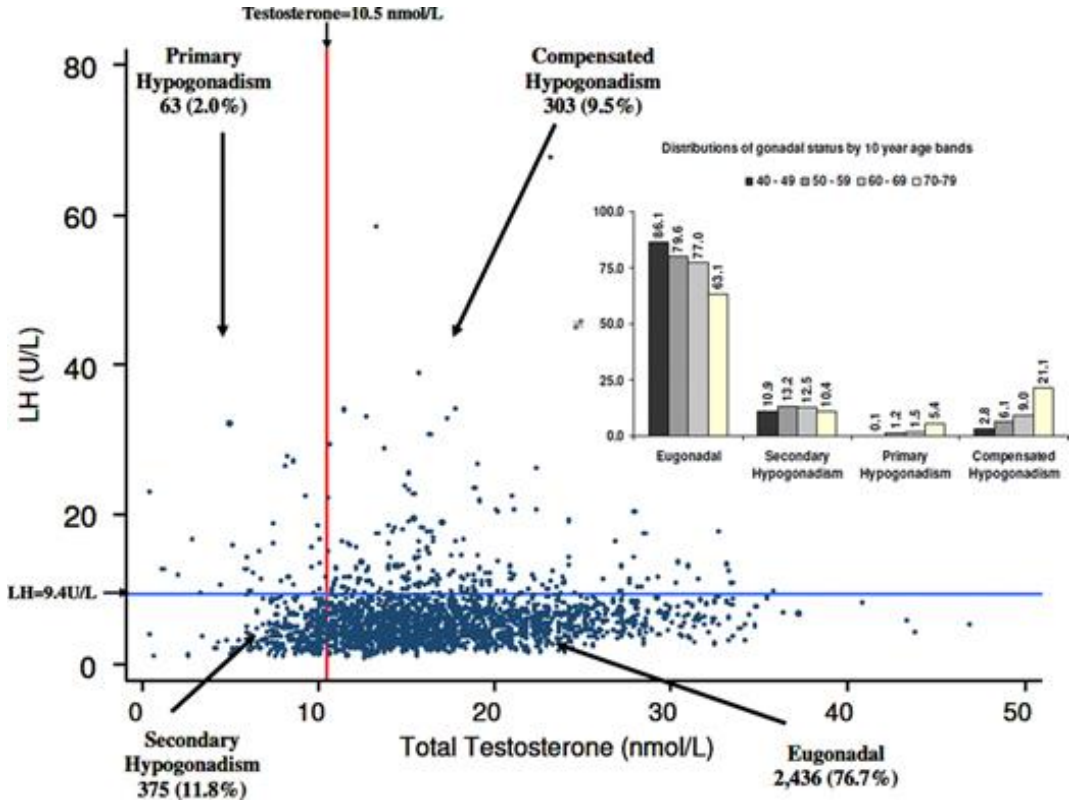
MARWA ELSAIED, PHARMD

DIRECTOR OF MEDICAL AFFAIRS

EMPOWER PHARMACY

Prevalence of Hypogonadism

- 3219 men analyzed between the ages of 40 to 79 years
  - 11.8% of the population had secondary hypogonadism
- 2162 men analyzed ≥45 years of age
  - 38.7% of the population had hypogonadism



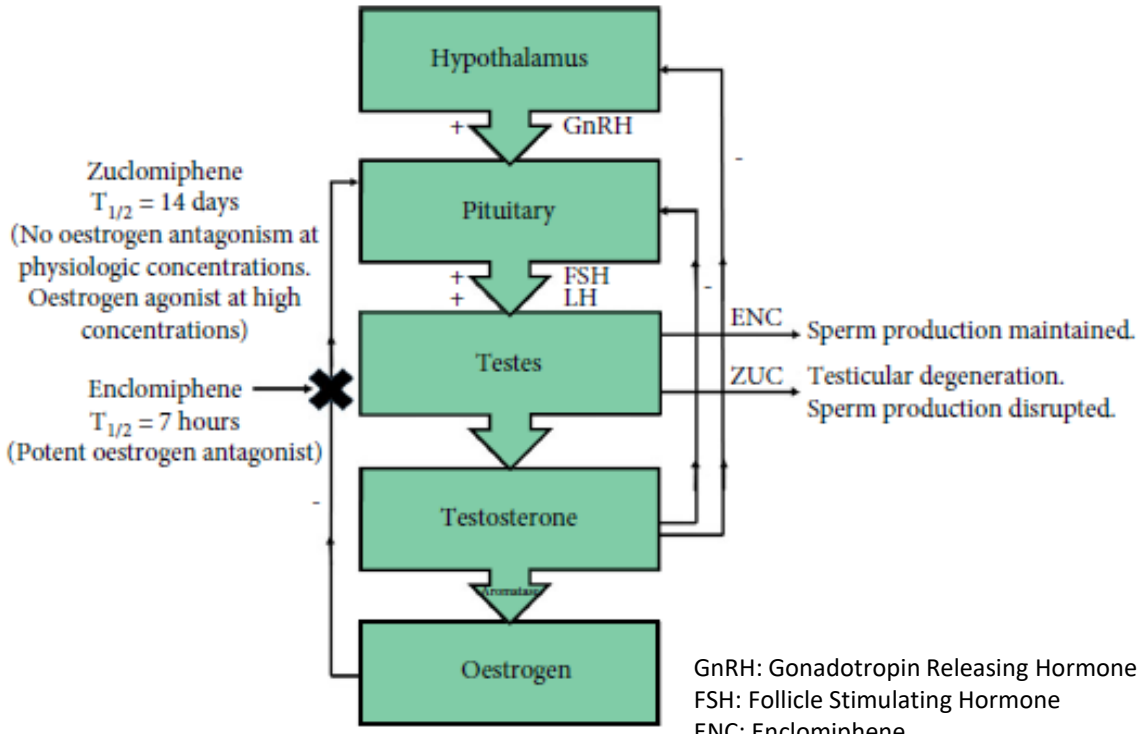
LH: Luteinizing Hormone

Abdelouahid Tajar,et al., Characteristics of Secondary, Primary, and Compensated Hypogonadism in Aging Men: Evidence from the European Male Ageing Study, *The Journal of Clinical Endocrinology & Metabolism*, Volume 95, Issue 4, 1 April 2010, Pages 1810–1818.
Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract. 2006 Jul;60(7):762-9.

Zuclomiphene

- Clomiphene contains 2 isomers
  - 62% enclomiphene
  - 38% zuclomiphene
- Zuclomiphene has a half-life ($T_{1/2}$) measured in days compared to Enclomiphene measured in hours
- Zuclomiphene is an estrogen agonist; Enclomiphene is an estrogen antagonist
- Zuclomiphene was found to disrupt sperm production
- The enclomiphene isomer, of the approved clomiphene drug, offers superior outcomes and lower risks than the zuclomiphene isomer
- Enclomiphene citrate has been studied for several decades for its use in secondary hypogonadism
  - Source: FDA Briefing Document; Pharmacy Compounding Advisory Committee (PCAC) Meeting; June 8, 2022, page 31

Fig. 1 Differential effects of isomers of clomiphene on testosterone and oestrogen antagonism.



GnRH: Gonadotropin Releasing Hormone
FSH: Follicle Stimulating Hormone
ENC: Enclomiphene
ZUC: Zuclomiphene

Fontenot GK, Wiehle RD, Podolski JS. Differential effects of isomers of clomiphene citrate on reproductive tissues in male mice. BJU Int. 2016 Feb;117(2):344-50.

Preclinical Studies

Author	Treatment Group	Subjects	Duration	Results	Authors Comments
Fontenot el al.	Placebo, 40mg/kg enclomiphene, 4mg/kg enclomiphene, 40mg/kg zuclomiphene, and 4mg/kg zuclomiphene.	Mice	90 days	Testicles, epididymis, seminal vesicles, and mice were all significantly decreased in weight in the zuclomiphene group compared to the enclomiphene group	*"The decreases in weight and function of reproductive tissues could be due to the oestrogenic effects of ZUC acting on the hypothalamic–pituitary–testes axis."*
Repros Theraputics	1.5mg/kg/day of zuclomiphene, enclomiphene, or clomiphene	Baboons	12 days	Clomiphene citrate significantly raised serum testosterone from 170 ng/dl to 559 ng/dl Enclomiphene raised serum testosterone from 170 ng/dl to 1144 ng/dl Zuclomiphene did not significantly impact testosterone levels	Zuclomiphene increased total cholesterol levels by 22% Enclomiphene reduced total cholesterol levels by 8%

Dog:
In a 9-month oral dog study (2, 10, and 40 which was reduced to 20 mg/kg/day due to morbidities associated with the 40 mg/kg/day dose treatment), a NOAEL of 2 mg/kg/day was reported.

Source: FDA Briefing Document; Pharmacy Compounding Advisory Committee (PCAC) Meeting; June 8, 2022, page 7

Earl JA, Kim ED. Enclomiphene citrate: A treatment that maintains fertility in men with secondary hypogonadism. Expert Rev Endocrinol Metab. 2019;14(3):157-165.
Podolski J, Wiehle R. Trans-clomiphene for the treatment of benign prostate hypertrophy, prostate cancer, hypgonadism, elevated triglycerides and high cholesterol. 2006 Google Patents

Safety Assessment

- As with all FDA approved testosterone therapies, thromboembolic events are noted
- "A number of adverse events that are known to be associated with testosterone replacement therapy were reported in the enclomiphene clinical studies." *2018 European Medicines Agency (EMA) Assessment Report*
- Pastuszak, et al analyzed data from 11 prospective, randomized, blind phase 2 and 3 trials on oral enclomiphene treatment
  - Enclomiphene = 953, Placebo = 290, T gel = 130
  - Hemoglobin and hematocrit were higher in men on T gel
  - Clinically insignificant increases in PSA were observed with enclomiphene
  - More significant and sustained decreases in total cholesterol, LDL, HDL

PSA: Prostate Specific Antigen

LDL: Low-Density Lipoprotein

HDL: High-Density Lipoprotein

Pastuszak, et al. COMPARISON OF THE EFFECTS OF ORAL ENCLOMIPHENE CITRATE AND TOPICAL TESTOSTERONE GELS TREATMENT ON SERUM HORMONES, ERYTHROCYTOSIS, LIPIDS, AND PROSTATE SPECIFIC ANTIGEN. Poster presenting at: SMSNA Annal Meeting; Nov 2015. Las Vegas, Nevada.

Endocrine Society Guidelines

"Hypogonadism is a clinical syndrome that results from failure of the testis to produce physiological concentrations of testosterone (T) (T deficiency) and/or **a normal number of spermatozoa** due to pathology at one or more concentrations of the hypothalamic–pituitary–testicular axis" - *The Journal of Clinical Endocrinology & Metabolism*

the proposed use. While studies may suggest that treatment with enclomiphene citrate may increase testosterone levels, with a concurrent increase in LH and FSH levels, it is unclear whether increasing testosterone concentrations alone in men with secondary hypogonadism equates to clinical effectiveness or confers clinical benefit. Clinical trials

Source: FDA Briefing Document; Pharmacy Compounding Advisory Committee (PCAC) Meeting; June 8, 2022, page 31

2.0 Treatment of hypogonadism with testosterone

2.1 We recommend testosterone therapy in hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency. (1|⊕⊕⊕O)

2.2 We recommend against testosterone therapy in men planning fertility in the near term or

Shalender Bhasin, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline, *The Journal of Clinical Endocrinology & Metabolism*, Volume 103, Issue 5, May 2018, Pages 1715–1744.

Guideline Statements

DIAGNOSIS AND TREATMENT OF INFERTILITY IN MEN: AUA/ASRM

"Initial evaluation of the male for fertility should include a reproductive history. (Clinical Principle) Initial evaluation of the male should also include one or more semen analyses (SAs). (Strong Recommendation; Evidence Level: Grade B)“

“The results of the SA should be used to guide management of the patient”

WHO LABORATORY MANUAL FOR THE EXAMINATION AND PROCESSING OF HUMAN SEMEN 6TH EDITION

"Semen examination is important for different reasons:

• assessment of male reproductive function and genital tract patency to enable appropriate treatment for male subfertility and to monitor treatment response;

• appraisal of fertility potential and choice of suitable treatment modality for an infertile couple"

It is important to note that sperm concentrations and other parameters assessed on semen analysis evaluate aspects of testicular function and are not tests of fertility.

Source: FDA Briefing Document; Pharmacy Compounding Advisory Committee (PCAC) Meeting; June 8, 2022, page 21

AUA: American Urological Association
ASRM: American Society of Reproductive Medicine
WHO: World Health Organization

Improvement in sperm parameters decreases time to conception

Table II

Summary of semen parameters, 5-year conception rate, and hazard ratios for 5-year conception within different categories of semen parameters based upon WHO cut-off values and our calculated thresholds (overall cohort, n = 6061).

Semen parameters	Cut points	N (%)	Conception rate (%, 95% CI)	Months to conception[1] (Median, 95% CI)	Hazard ratio[2] (95% CI)	Concordance[2]
WHO cut-offs						
Concentration						0.565
	<15 M/ml	687 (11%)	56.5 (52.7, 60.5)	39.0 (30.4, 46.9)	1.00 (Ref)	
	≥15 M/ml	5369 (89%)	68.7 (67.4, 70.0)	20.8 (19.6, 22.1)	1.49 (1.32,1.68)	
Progressive motility						0.572
	<32%	1227 (20%)	56.4 (53.6, 59.4)	37.9 (33.2, 46.3)	1.00 (Ref)	
	≥32%	4834 (80%)	70.0 (68.7, 71.4)	19.6 (18.3, 20.8)	1.48 (1.35,1.63)	
Total sperm count						0.568
	<39 M	741 (12%)	54.6 (51.0, 58.5)	43.4 (35.5, 53.3)	1.00 (Ref)	
	≥39 M	5320 (88%)	69.0 (67.7, 70.4)	20.3 (19.3, 21.5)	1.52 (1.35,1.71)	

Keihani S, Verrilli LE, Zhang C, Presson AP, Hanson HA, Pastuszak AW, Johnstone EB, Hotaling JM. Semen parameter thresholds and time-to-conception in subfertile couples: how high is high enough? Hum Reprod. 2021 Jul 19;36(8):2121-2133.

Merck Product Status Report

Last Update: May 13, 2022

Product Description	NDC #	Material	Product Status	Notes
ANTIVENIN BWS (Latrodectus mactans) Vial to yield 2.5 mL of restored serum	00006-5424-02	1029675	See Notes	Product is available for drop-ship for up to 2 per order
BCG VACCINE for percutaneous use Single-use vial	00052-0603-02	1013308	Backordered	Updated shipping information will be provided as available
PREGNYL (chorionic gonadotropin) for injection USP 10,000 U, 10mL vial	00052-0315-10	1022691	On Allocation	Product being allocated
TICE BCG BCG LIVE for intravesical use Single-use vial	00052-0602-02	1013307	On Allocation	Product being allocated

This report is for business planning purposes and intended for the sole use of customers purchasing pharmaceutical and/or vaccine products directly from Merck. The terminology used herein may not always be consistent with FDA or other Regulatory terms or definitions. This report is not intended for use by any Regulatory Agency. All required product shortage notifications will be made in compliance with applicable regulations, directly to the FDA and/or any other applicable agency. In addition, similar Merck product status information will be provided to the American Society of Health-System Pharmacists (ASHP), which also tracks product shortages.

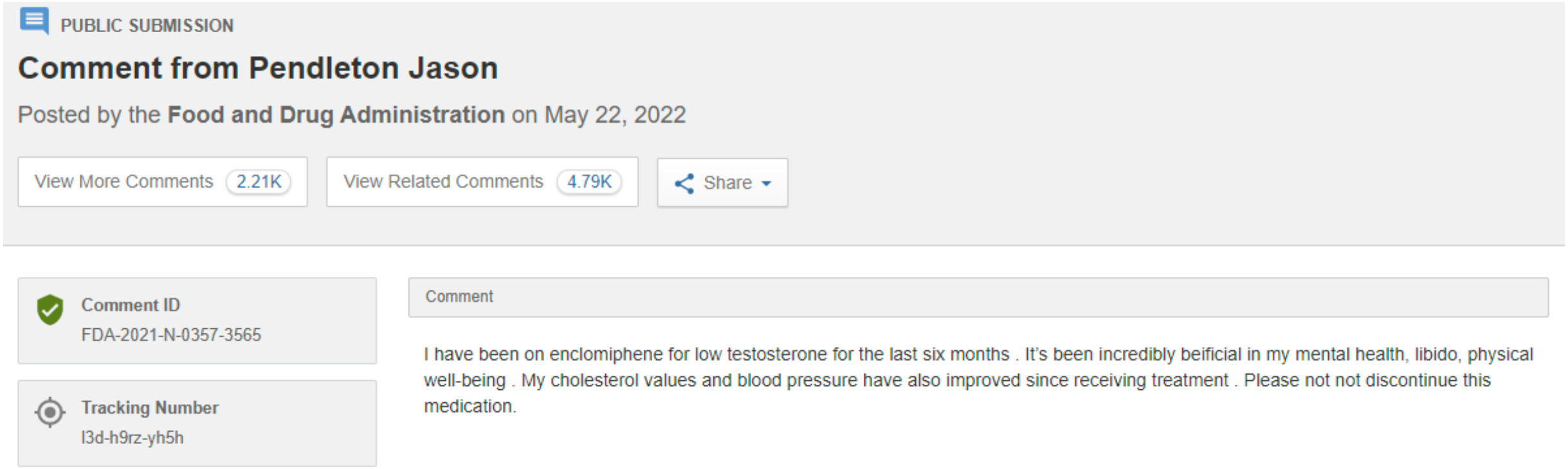
Accessed June 1st, 2022

Enclomiphene vs. Testosterone

	Testosterone Replacement Therapy (TRT)	Enclomiphene
Transference risk	Yes	No
Supranormal T levels	Yes	No
Suppressed spermatogenesis	Yes	No
Suppressed testicular function	Yes	No
Testis atrophy	Yes	No

Enclomiphene answers patients unmet need for therapy that does not compromise fertility

Patient Testimonial



PUBLIC SUBMISSION

Comment from Pendleton Jason

Posted by the **Food and Drug Administration** on May 22, 2022

View More Comments 2.21K | View Related Comments 4.79K | Share

Comment ID
FDA-2021-N-0357-3565

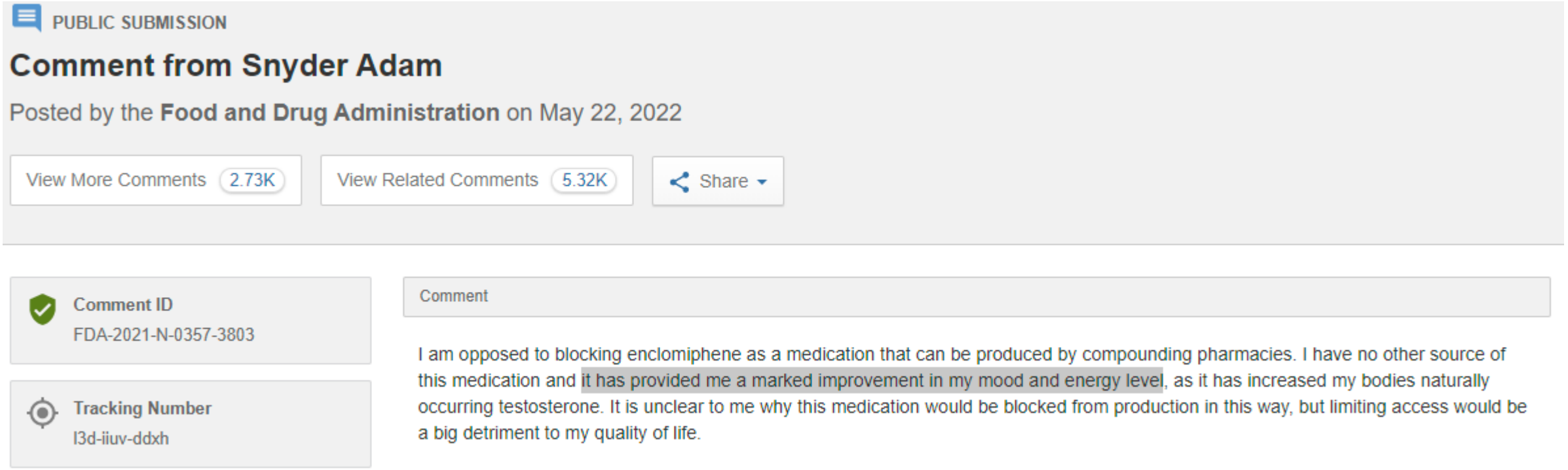
Tracking Number
l3d-h9rz-yh5h

Comment

I have been on enclomiphene for low testosterone for the last six months . It's been incredibly beificial in my mental health, libido, physical well-being . My cholesterol values and blood pressure have also improved since receiving treatment . Please not not discontinue this medication.

Source: https://www.regulations.gov/document/FDA-2021-N-0357-2586

Patient Testimonial



PUBLIC SUBMISSION

Comment from Snyder Adam

Posted by the **Food and Drug Administration** on May 22, 2022

View More Comments 2.73K | View Related Comments 5.32K | Share

Comment ID
FDA-2021-N-0357-3803

Tracking Number
l3d-iiuv-ddxh

Comment

I am opposed to blocking enclomiphene as a medication that can be produced by compounding pharmacies. I have no other source of this medication and it has provided me a marked improvement in my mood and energy level, as it has increased my bodies naturally occurring testosterone. It is unclear to me why this medication would be blocked from production in this way, but limiting access would be a big detriment to my quality of life.

Source: https://www.regulations.gov/document/FDA-2021-N-0357-2586

Patient Testimonial

PUBLIC SUBMISSION

Comment from Anonymous

Posted by the **Food and Drug Administration** on May 22, 2022

View More Comments 2.73K | View Related Comments 5.32K | Share

Comment ID
FDA-2021-N-0357-3797

Tracking Number
l3d-nyp8-ei8c

Comment Details | Submitter Info

Comment

I have been taking enclomiphene for aproximately 8 months daily. I am a young man (mid 20s) who tested really low t (204 ng/dl) and undetectable estrogen. I had all the symptoms of low t. Enclomiphene has been extremely beneficial by boosting my own body to produce more testosterone without having to resort to using exogenous testosterone. I am married and want to have children in my future, I don't want to be forced to lose my fertility if this medication is no longer available. Enclomiphene is a much better variant of Clomid. The reason its much better is because it has no side effects like clomid does. I have had so much more energy, will power, and sex drive since I started Enclomiphene. My testosterone and estrogen levels are back to normal and I've gone from about 25% body fat to about 19%. Removing enclomiphene from the list of medications that can be produced by compounding pharmacies would be a devastating blow to my life and many men's lives around the country.

Source: https://www.regulations.gov/document/FDA-2021-N-0357-2586

Conclusions

- Enclomiphene is part of an FDA approved medication
- Adverse events notated are associated with all exogenous testosterone therapy; mitigated with provider education
- Exogenous testosterone therapy impairs sperm production
- Improved semen parameters are indicative of improved probability and time to conception
- Patient comments, on the FDA Docket, illustrate the improvement in signs and symptoms of hypogonadism with the use of Enclomiphene

Thank you!

References

- FDA Briefing Document; Pharmacy Compounding Advisory Committee (PCAC) Meeting; June 8, 2022. https://www.fda.gov/media/158541/download. Accessed May 24, 2022.
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- World Health Organization . WHO Laboratory Manual for the Examination and Processing of Human Semen. 6th ed. WHO Press; Geneva, Switzerland: 2021. [(accessed on 24 May 2022)].
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Enclomiphene citrate

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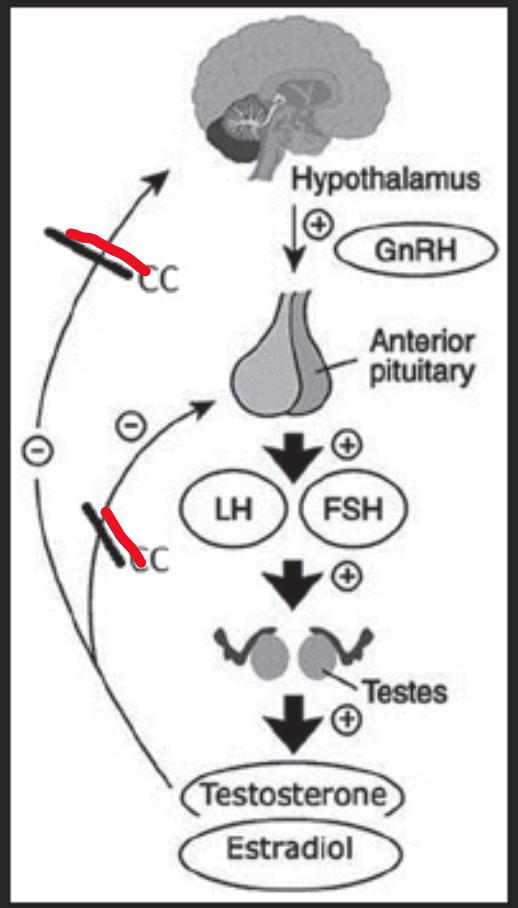
PRESENTING ON BEHALF OF EMPOWER PHARMACY

Mechanism of Action



https://www.excelmale.com/testosterone-the-new-how-much-do-you-bench/

Clomiphene citrate (t ½ : 10 hours)

Stereoisomers

(cis) zuclomiphene citrate

Estrogen receptor agonist

Estrogenic side effects

t ½ : 30 days

(trans) enclomiphene citrate

FSH and LH

t ½: 10 hours

FSH: follicle-stimulating hormone; LH: luteinizing hormone

Pharmacodynamics and Pharmacokinetics

Non-dose-dependent steady-state= 25 mg/day dose.

Maximum serum drug concentration= 2-3h after ingestion

First order elimination

Hepatic metabolization (CYP2D6)

Enteric elimination and enterohepatic recirculation.

FSH and LH persisted elevated after 7d

Clinical Efficacy

Phase I

- Clomiphene vs Enclomiphene (EC) vs Zuclomiphene
- Clomiphene: 170 ng/dl to 559 ng/dl
- Enclomiphene: 170 ng/dl to 1,144 ng/dl (p=0.03)
- X FSH and LH levels
- Enclomiphene:

✓↓ 8% cholesterol

✓↓ Platelets and granulocytes

✓↑ lymphocytes and eosinophils

Phase II

- Opened-label
- 12 hypogonodal men
- Testosterone vs enclomiphene
- 3m after therapy:

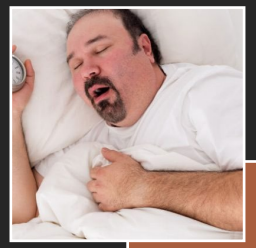
✓T: <12 mill/ml

✓EC: ≥75 mill/ml and ↑ FSH and LH.

- Double blinded: T vs EC 12.5mg vs EC 25mg
- 73 hypogonodal males

✓All increased T

✓↑↑ in FSH and LH with EC 25 mg



Phase III

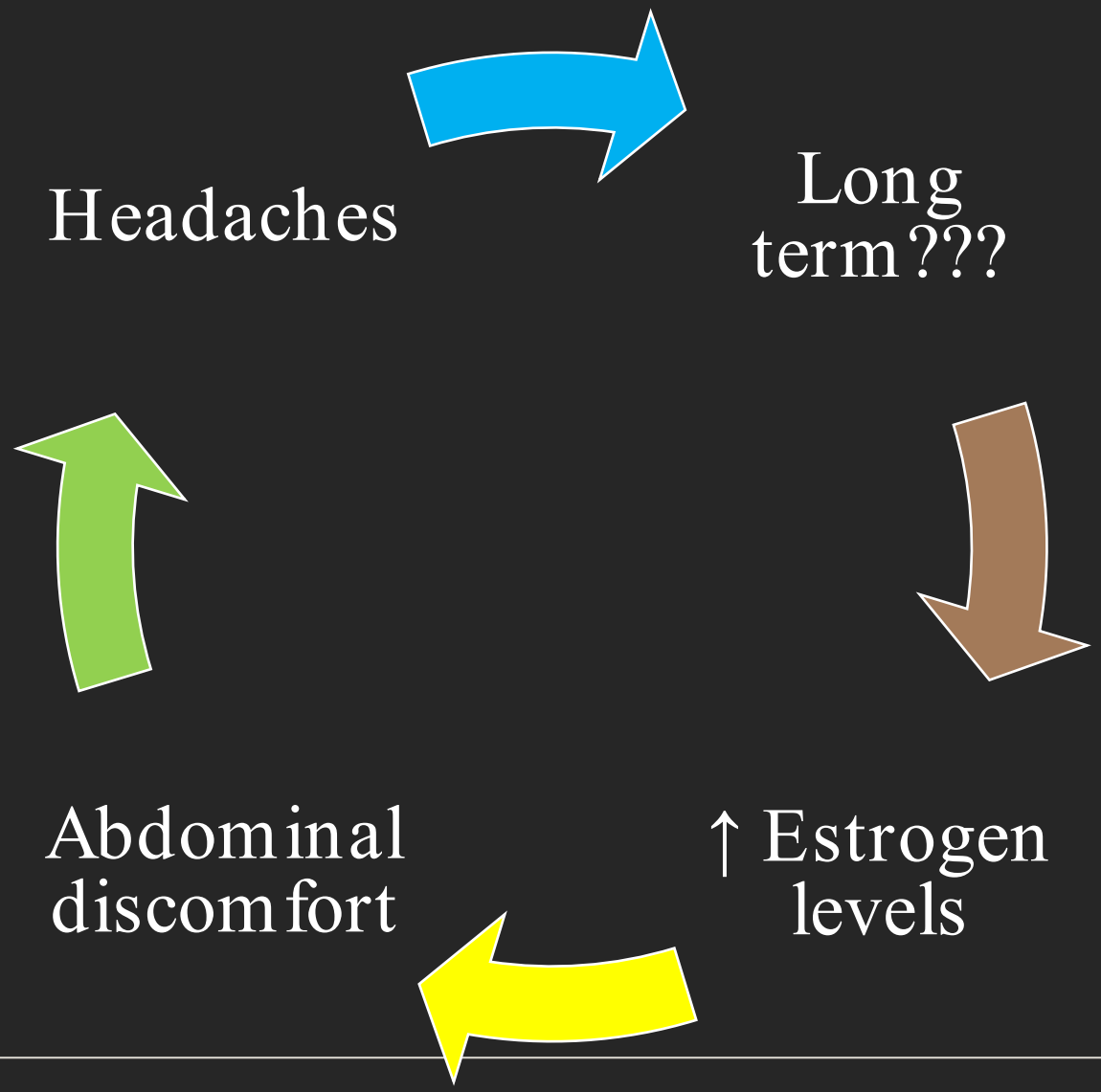
- Randomized, double-blind, placebo-controlled trial
- 265 overweight men 18–60 years
- Testosterone gel(TG) vs EC vs placebo

✓↑ in T with EC and TG

✓EC: ↑ sperm count

✓TG: ↓ sperm count

Side Effects



Clinical Use

In the US: for every 100 couples, 12-13 have fertility issues

Male infertility accounts for ~1/3

Medical therapy for male factor infertility

- Very expensive
- Difficult accessibility

Human chorionic gonadotropin (hCG)

Clomiphene citrate (CC)

Enclomiphene citrate (EC)

Our Clinical Experience

We started formulating **enclomiphene** on Nov 2021

Medical indications:

- Hypogonadism
- Azoospermia
  Oligospermia
- Normal testosterone level with hypogonadal symptoms

~160 patients have started treatment with enclomiphene
(Nov 2021 – May 2022)

Our Clinical Experience – Hormones

Table 1. Paired t-test of hormone levels after ~3 months under enclomiphene treatment.

Hormones	N	Pre-treatment (mean)	Post-treatment (mean)	*P*-value
Testosterone (ng/ dL)	16	558.14	740.94	0.031
FSH (ng/ dL)	9	6.34	8.2	0.26
LH (ng/ dL)	9	4.11	11.2	0.004
E (pg/ Ml)	11	34.36	41.46	0.24
17-OH (ng/ dL)	8	58.1	107	0.076

Our Clinical Experience – Semen analysis

Table 2. Paired t-test of semen analysis parameters after ~3 months under enclomiphene treatment.

Semen analysis parameter	N	Pre-treatment (mean)	Post-treatment (mean)	*P*-value
Volume (mL)	13	2.36	2.46	0.40
Concentration (mill/ mL)	13	4.95	12.65	<0.001
Motility (%)	13	23.45	41.25	0.009
Total motile sperm count	13	3.36	13.71	0.05

Our Clinical Experience – Symptomatology

30 patients have had follow-up

66% improvement of all symptoms

10% improvement or 2 or less symptoms

20% no improvement in symptoms

Our Clinical Experience – Side Effects

- Weight gain: 3 (9.6%) patients
- Gynecomastia: 1 (3.2%) patient
- Dry mouth: 1 (3.2%) patient

Retrospective chart review of 69 of our patients currently on enclomiphene showed that 22 (31.9%) were previously on clomiphene and stopped it due to side effects

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Thank You

GLUTATHIONE

Pharmacy Compounding Advisory Committee Meeting
June 8, 2022

A.J. Day, PharmD
Vice President of Clinical Services
PCCA

Presenting on behalf of PCCA & NCPA

FDA evaluation, pg 4

1. *Stability of the active pharmaceutical ingredient (API) and likely dosage forms*

As a solid, glutathione is stable at room temperature when carefully kept away from oxygen. According to the revised Generally Recognized as Safe (GRAS) notices regarding glutathione for use as a food ingredient,[6] glutathione is stable when kept in an airtight container at room temperature and normal relative humidity levels for up to 39 months. Only 65 - 80% of glutathione remains unchanged in aqueous solutions with various pH values after 7 days at room temperature. The instability of glutathione in solutions may be due to the rapid oxidation of the thiol group into a disulfide group (Harbin et al. 2004). However, with proper formulation techniques, sufficient stability of the aqueous formulations can also be achieved. For example, a reduced glutathione solution at an initial concentration of 189 mg/ml was stored under 5 °C at pH 6.4 (0.005M octylammonium orthophosphate buffer) for 112 days. No decrease in the concentration of the reduced glutathione was observed (Harbin et al. 2004). Therefore, glutathione is likely to be stable under room temperature in its solid formulations (capsules, oral and sublingual troche, etc.) when protected from oxygen. Similarly, with protection from oxygen and proper formulation techniques (e.g., proper buffer solutions, controlled pH and temperature), the substance can be stable when compounded as liquid formulations (such as injection and oral solutions) and semi-solid formulations (e.g., creams, gels, etc.).

2. *Probable routes of API synthesis*

Glutathione can be synthesized from yeast fermentation, followed by centrifugation, complexation, ultrafiltration, ion exchange, washing and recrystallization (Li et al. 2004).

FDA evaluation, pg 5

Likely impurities include:

- Residual starting materials and reaction intermediates from fermentation
- Bioburden, such as residual yeast
- Glutathione disulfide from the oxidation of glutathione

4. *Toxicity of those likely impurities*

The impurities mentioned above are unlikely to be present at a highly toxic level.

5. *Physicochemical characteristics pertinent to product performance, such as particle size and polymorphism*

Glutathione is a white solid that is soluble in water. No further information on the influence of particle size and polymorphism on bioavailability were found in the literature.

SAFETY EVALUATION

FDA Safety/Non-clinical Assessment, pg 15

Conclusions: Glutathione is a tripeptide that is endogenously synthesized in the human body. The pharmacology and metabolism of glutathione is well understood. However, insufficient nonclinical data exist to evaluate the toxicity profile of glutathione in repeat dose toxicity or developmental toxicity. Available acute toxicity studies in animals show that high levels of glutathione are tolerated. Available genotoxicity data from the Ames assay and the mouse lymphoma assay show that glutathione is not mutagenic in the absence of metabolic activation. Glutathione inhibited experimentally induced oral carcinogenesis in glutathione-treated hamsters.

Glutathione has been tested for its potential protective activity in animal models of diseases. Publicly available literature has reported on the potential use of glutathione in animal models. These include a link between glutathione dosing and a decrease in neuropathy in cisplatin treated rats when compared to control animals. In another animal model, IV injection of GPx was reported to provide mice with protection against a lethal dose of acetaminophen. The applicability of these findings to the clinical setting is not known at this time.

FDA conclusion on Safety, pg 24

IV administration of glutathione has resulted in hepatotoxicity and life-threatening anaphylaxis, despite rapid elimination from systemic circulation. One clinical study of the use of nebulized, oral inhalation of glutathione for asthma identified significant safety concerns in this population (Marrades et al. 1997). Oral glutathione is minimally absorbed and appears to be associated primarily with local, gastrointestinal adverse effects. Due to these significant safety concerns, particularly with respect to IV and inhalation formulations, FDA recommends that glutathione not be added to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.

- Hepatotoxicity is only cited in FDA's evaluation in a letter to the editor case study which does not show causality for glutathione
- Anaphylaxis is not cited in any clinical trials reviewed for any proposed use

Hepatotoxicity: Naito 2010

- Letter To The Editor
- "…he was anxious concerning disease progression and consulted another private clinic that he found on an internet service, from which he received intravenous GSH (1,200 mg daily) injection per week…"
- No information provided to the quality, stability, and source of the glutathione

Hepatoxicity: One case (a literature case report from Japan; Naito et al. 2010) reported "hepatotoxicity." The patient was receiving glutathione 1200 mg IV/day administered once a week for Parkinson's disease, in addition to three other medications for his Parkinson's disease (e.g., entacapone) and nine additional concomitant medications. After five months of treatment (estimated exposure to glutathione 24,000 mg), the patient reported malaise and anorexia and was hospitalized. The patient had an elevated aspartate aminotransferase (AST) of 1,040 IU/L (normal AST range: 10-34 IU/L) and alanine aminotransferase (ALT) of 890 IU/L (normal ALT range: 10-40 IU/L). Five days after all medications except for L-dopa/DCI 300 mg/day were discontinued, the patient's hepatic enzymes decreased to 241 IU/L (AST) and 595 IU/L (ALT). Hepatic injury resolved within two months. The drug-induced lymphocyte stimulation test (DLST) result for entacapone was negative but equivocally positive for glutathione. It should be noted that the DLST is a test commonly used in Japan to test for drug hypersensitivities; however, false-positive and false-negative results may occur (Saito et al. 2018).

GSH: reduced glutathione

Anaphylaxis 1, FAERS

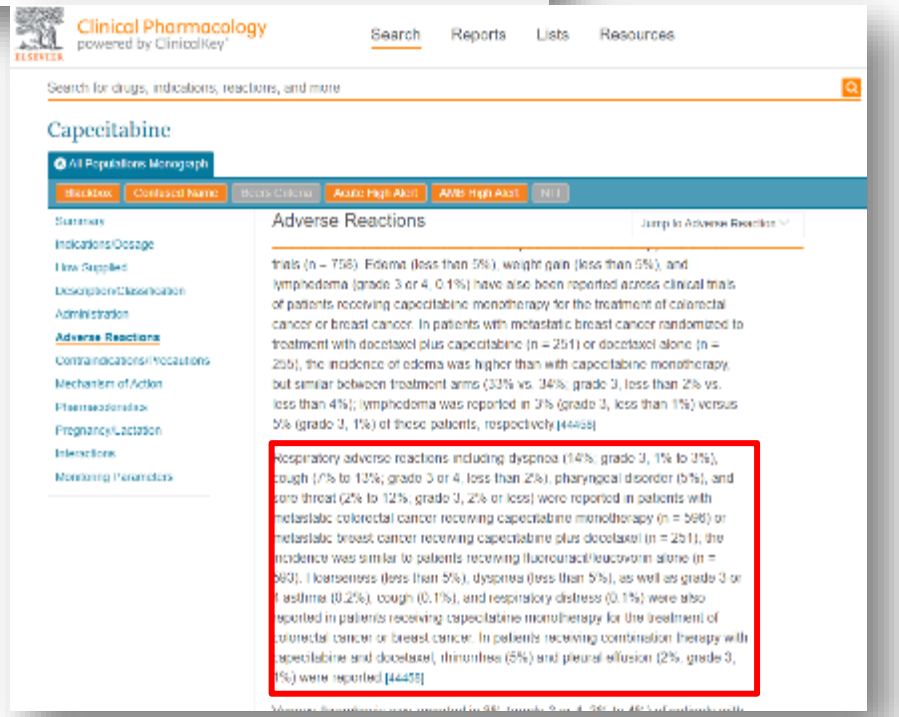
- FAERS and CAERS cannot show causality
  - FAERS shows 15 cases over 22 years *associated* with glutathione
  - Cases often do not report doses or source of glutathione (online-sourced injections vs. prescription compounded formulations)

The anaphylactic reaction that occurred in the U.S. was in a 19 year old female patient with a latex sensitivity who received an unknown dose of glutathione IV for the treatment of Lyme disease. She experienced the anaphylactic reaction 30 minutes after starting the infusion and was treated with epinephrine, diphenhydramine IV and steroids IV. The day following the initial anaphylactic reaction to glutathione, the patient experienced anaphylaxis to ceftriaxone IV, despite previously tolerating seven weeks of ceftriaxone. Ten days after the initial anaphylactic episode, the patient was re-challenged with an unknown dose of IV glutathione and she had anaphylaxis that required cardiopulmonary resuscitation. The source of the glutathione was not disclosed.

FAERS: FDA Adverse Event Reporting System
CAERS: Center for Food Safety and Nutrition Adverse Event Reporting System

Anaphylaxis 2, FAERS

The anaphylaxis case that occurred in China was in a 55 year old male patient who developed pharyngeal edema, cyanosis and airway "whistling" during his first infusion of glutathione 2400 mg IV for the treatment of rectal cancer. The patient was also started on oral capecitabine 200 mg on the same day (timing related to anaphylaxis event is unclear). Both glutathione and capecitabine were discontinued. The patient received IV saline, dexamethasone 10 mg, calcium gluconate, and aminophylline 250 mg IV infusion. A few hours later the patient's vitals normalized.



Source: https://www.clinicalkey.com/pharmacology/

Clinical Pharmacology: Capecitabine

Respiratory adverse reactions including dyspnea (14%; grade 3, 1% to 3%), cough (7% to 13%; grade 3 or 4, less than 2%), pharyngeal disorder (5%), and sore throat (2% to 12%; grade 3, 2% or less) were reported in patients with metastatic colorectal cancer receiving capecitabine monotherapy (n = 596) or metastatic breast cancer receiving capecitabine plus docetaxel (n = 251); the incidence was similar to patients receiving fluorouracil/leucovorin alone (n = 593). Hoarseness (less than 5%), dyspnea (less than 5%), as well as grade 3 or 4 asthma (0.2%), cough (0.1%), and respiratory distress (0.1%) were also reported in patients receiving capecitabine monotherapy for the treatment of colorectal cancer or breast cancer. In patients receiving combination therapy with capecitabine and docetaxel, rhinorrhea (5%) and pleural effusion (2%; grade 3, 1%) were reported.[44458]

Source: https://www.clinicalkey.com/pharmacology/

FDA conclusion on Safety, pg 24

IV administration of glutathione has resulted in hepatotoxicity and life-threatening anaphylaxis, despite rapid elimination from systemic circulation. One clinical study of the use of nebulized, oral inhalation of glutathione for asthma identified significant safety concerns in this population (Marrades et al. 1997). Oral glutathione is minimally absorbed and appears to be associated primarily with local, gastrointestinal adverse effects. Due to these significant safety concerns, particularly with respect to IV and inhalation formulations, FDA recommends that glutathione not be added to the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act.

Marrades 1997

- 8 patients, randomized, double-blind, cross-over, placebo-control
- 600mg glutathione nebulized at same time of day, 1 week apart
  - No information on quality of starting material (provided by MD in NY,NY while study conducted in Barcelona, Spain; no potency or identity testing of the formulation)
- pH of GSH solution = 3.0

Glutathione Preparation

Glutathione solution (600 mg · vial^{-1}) was kindly provided by R. G. Crystal, M.D. (New York, NY), and reconstituted with 4 ml of 0.9% NaCl. We used this dosage based on previous studies (6) that showed an increased antioxidant effect on the airway fluid lining. Four milliliters of this solution were placed in the reservoir of a pneumatic nebulizer (Ultravent; Mallinckrodt, St. Louis, MO) that generates aerosol droplets appropriate for alveolar deposition. The size of aerosol droplets, determined by laser particle-size analysis, indicated a mass median aerodynamic diameter of 2.8 μm with a geometric SD of 1.3 μm. The nebulizer was driven at 40 psi (1 psi = 6.9 kPa) with compressed air to generate 10 L · min^{-1} of aerosol. Using a one-way valve, noseclip and mouthpiece in series, the system was closed; that is, all gas, including aerosolized GSH, was either inspired or expired through a filter to collect all expired drug. Using this system, aerosolization of 600 mg GSH to spontaneously breathing individuals with the nostrils occluded required 25 min. The pH and osmolarity of the GSH solution were 3.0 and 660 mosm · kg^{-1}, respectively. Osmolarity was measured with an osmometer (Advanced Micro-Osmometer model 3MO-Plus; Advanced Instruments, Inc., Norwood, MA). Using this delivery system, Holroyd and co-workers reported (7) that the percentage of reduced GSH in the preparation was above 97% and remained unchanged following aerosolization.

Marrades 1997 (continued)

To explain the bronchoconstrictor effect of nebulized GSH in our patients, we suggest two potential hypotheses. The most salient could be a result of the fact that GSH is a highly hydrophilic substance containing cysteine, an aminoacid with a sulfhydryl group. When either sulfur species dissolves in aqueous solutions, a pH-dependent equilibrium is established among

different sulfites (sulfur dioxide [SO_2], metabisulfite [$SO_5^=$], bisulfite [SO_3^-], sulfite [$SO_3^=$]) (18). These sulfites produce the characteristic "rotten eggs" smell of GSH solution, and their acute bronchoconstrictor effects are well established. In healthy subjects, however, this effect was significant only after inhalation of concentrations in excess of 5 parts per million, or ppm (19). Several studies have shown that patients with asthma are exquisitely sensitive to the bronchomotor effects of sulfites (concentrations below 1 ppm). The precise mechanism of SO_2-induced bronchoconstriction remains elusive, and both cholinergic and noncholinergic mechanisms have been implicated (20, 21). Recently, a sensory nerve activation with tachykinins also has been invoked (22). It has been suggested that when sulfites are inhaled from a mouthpiece, as in our study, their bronchoconstrictor effects could increase (23). Although we did not measure the levels of sulfites during GSH nebulization, it is likely that they could be implicated in the induced bronchoconstriction. The finding that all the patients tested showed a significant bronchoconstrictive response to metabisulfite challenge, correlated inversely with the threshold of responsiveness to GSH, lends further support to the mechanism of bronchoconstriction induced by sulfite formation. The lack of adverse reaction to GSH nebulization in either IPF patients or HIV-seropositive individuals could be related to the different bronchoconstrictor sensitivity to sulfites of these populations.

Marrades 1997 (continued)

Glutathione Preparation

Glutathione solution (600 mg · vial^{-1}) was kindly provided by R. G. Crystal, M.D. (New York, NY), and reconstituted with 4 ml of 0.9% NaCl. We used this dosage based on previous studies (6) that showed an increased antioxidant effect on the airway fluid lining. Four milliliters of this solution were placed in the reservoir of a pneumatic nebulizer (Ultravent; Mallinckrodt, St. Louis, MO) that generates aerosol droplets appropriate for alveolar deposition. The size of aerosol droplets, determined by laser particle-size analysis, indicated a mass median aerodynamic diameter of 2.8 μm with a geometric SD of 1.3 μm. The nebulizer was driven at 40 psi (1 psi = 6.9 kPa) with compressed air to generate 10 L · min^{-1} of aerosol. Using a one-way valve, noseclip and mouthpiece in series, the system was closed; that is, all gas, including aerosolized GSH, was either inspired or expired through a filter to collect all expired drug. Using this system, aerosolization of 600 mg GSH to spontaneously breathing individuals with the nostrils occluded required 25 min. The pH and osmolarity of the GSH solution were 3.0 and 660 mosm · kg^{-1}, respectively. Osmolarity was measured with an osmometer (Advanced Micro-Osmometer model 3MO-Plus; Advanced Instruments, Inc., Norwood, MA). Using this delivery system, Holroyd and co-workers reported (7) that the percentage of reduced GSH in the preparation was above 97% and remained unchanged following aerosolization.

FDA stability evaluation, pg 4

1. Stability of the active pharmaceutical ingredient (API) and likely dosage forms

As a solid, glutathione is stable at room temperature when carefully kept away from oxygen. According to the revised Generally Recognized as Safe (GRAS) notices regarding glutathione for use as a food ingredient,[6] glutathione is stable when kept in an airtight container at room temperature and normal relative humidity levels for up to 39 months. Only 65 - 80% of glutathione remains unchanged in aqueous solutions with various pH values after 7 days at room temperature. The instability of glutathione in solutions may be due to the rapid oxidation of the thiol group into a disulfide group (Harbin et al. 2004). However, with proper formulation techniques, sufficient stability of the aqueous formulations can also be achieved. For example, a reduced glutathione solution at an initial concentration of 189 mg/ml was stored under 5 °C at pH 6.4 (0.005M octylammonium orthophosphate buffer) for 112 days. No decrease in the concentration of the reduced glutathione was observed (Harbin et al. 2004). Therefore, glutathione is likely to be stable under room temperature in its solid formulations (capsules, oral and sublingual troche, etc.) when protected from oxygen. Similarly, with protection from oxygen and proper formulation techniques (e.g., proper buffer solutions, controlled pH and temperature), the substance can be stable when compounded as liquid formulations (such as injection and oral solutions) and semi-solid formulations (e.g., creams, gels, etc.).

Marrades 1997 (continued)

Review

The Treatment of Pulmonary Diseases and Respiratory-Related Conditions with Inhaled (Nebulized or Aerosolized) Glutathione

Jonathan Prousky[1,2]

- Other researchers do not share FDA's evaluation
- Prousky 2008 (review article)

able to prepare the solution of GSH at the desired concentrations. The typical dosages used in the studies cited in Table 3 were 600 mg once daily, 600 mg twice daily, 900 mg daily, 1350 mg daily or a daily dose of 66 mg/kg of body weight. Better results are more likely to be achieved with doses of at least 600 mg or more each day. One of the studies used much larger doses (66 mg/kg of body weight) since the authors speculated that these would be necessary to replace half of the amount of GSH that is produced each day (e.g. a 150 lb male synthesizes 10 g daily and would need 5 g as a replacement dose) (27). When patients are unresponsive to doses in the range of 600–1350 mg per day, it might be suitable to try doses that would replace half the estimated amount of GSH that is synthesized each day. These gram doses might yield better clinical results.

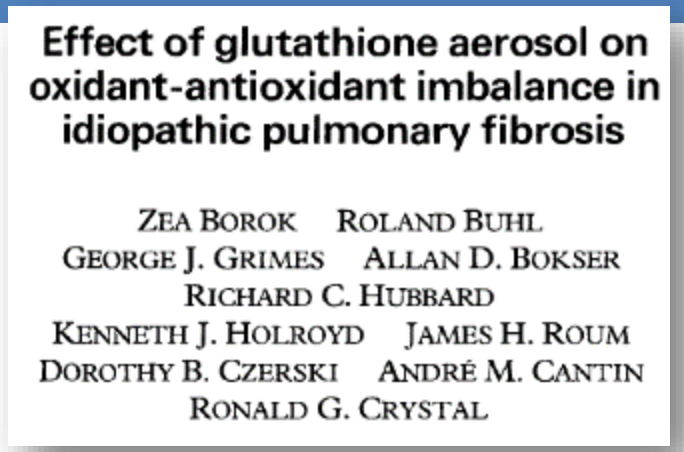
In terms of side effects, GSH inhalation is very safe. Minor side effects such as mild coughing and an unpleasant odor were reported in some of the studies included in this review. These minor side effects, better described as mild nuisance problems, were not severe enough to cause any of the study participants to discontinue treatment with inhaled GSH. The only worrisome or potentially life-threatening side effect to note is bronchoconstriction, which would be more likely to occur among sulfite-sensitive asthma and MCSD patients. However, if proper precautions such as sulfite testing are done prior to treatment, this serious side effect should be avoidable.

Monitoring the Clinical Response to Inhaled GSH

For pulmonary diseases or respiratory-related conditions, baseline pulmonary function testing with a spirometer or a simple peak flow meter is recommended prior to the

MCSD: multiple chemical sensitivity disorder

Borok 1991


Effect of glutathione aerosol on oxidant-antioxidant imbalance in idiopathic pulmonary fibrosis

ZEA BOROK ROLAND BUHL
GEORGE J. GRIMES ALLAN D. BOKSER
RICHARD C. HUBBARD
KENNETH J. HOLROYD JAMES H. ROUM
DOROTHY B. CZERSKI ANDRÉ M. CANTIN
RONALD G. CRYSTAL

- 10 patients, 19 controls
- 600mg glutathione aerosol inhalation q12h for 3 days
- "Detailed safety evaluations were done throughout the study."
- "The therapy was lung-specific, since plasma glutathione did not change."
- "This feasibility study demonstrates that aerosol therapy of IPF with glutathione is safe, and has "biologic efficacy"…"

*Identified as "short report" – specific safety measures not published

Source: https://www.thelancet.com/journals/lancet/article/PII0140-6736(91)90350-X/fulltext

IPF: idiopathic pulmonary fibrosis

Holroyd 1993

- Glutathione 600mg BID x 3 days
- 14 patients

Thorax 1993;48:985–989

Correction of glutathione deficiency in the lower respiratory tract of HIV seropositive individuals by glutathione aerosol treatment

Kenneth J Holroyd, Roland Buhl, Zea Borok, James H Roum, Allan D Bokser, George J Grimes, Dorothy Czerski, Andre M Cantin, Ronald G Crystal

To evaluate possible toxicity of the glutathione aerosol, symptoms, physical examination, routine blood studies, chest radiograph, electrocardiogram, renal function, arterial blood gases, and tests of pulmonary function (forced vital capacity, forced expiratory volume in one second, total lung capacity, diffusing capacity) were followed carefully throughout the study. In addition, visual examination of the respiratory mucosa and analysis of differential cell count in bronchoalveolar lavage fluid were performed before the first and after the last aerosol doses.

GLUTATHIONE PREPARATION

The reduced form of glutathione was obtained as a free acid (tissue culture grade; Sigma) and stored at 4°C. All preparations were sterile and pyrogen-free as determined by the NIH Pharmaceutical Development Service. The glutathione preparation was >98% pure. The percentage of reduced glutathione determined before each experiment (see below) was constantly >96%.

Results

SAFETY EVALUATION

No symptoms referable to the aerosol administration of glutathione were noted, and physical examination and all clinical measurements remained stable following treatment with glutathione. Pulmonary function tests and arterial blood gases were also unchanged (all indices $p > 0{\cdot}3$ compared with baseline). Aerosolisation of reduced glutathione did not cause inflammation of the lower respiratory tract as judged by visual inspection of the mucous membranes, measurements of volumes of epithelial lining fluid in bronchial lavage fluids before and after aerosol administration, or lavage differential cell count (all comparisons $p > 0{\cdot}1$ compared with baseline values).

BID: twice daily
NIH: National Institutes of Health

Wang 2021

- 7 studies, meta-analysis
- 450 patients total

EXPERIMENTAL AND THERAPEUTIC MEDICINE 21: 125, 2021

Potential use of glutathione as a treatment for Parkinson's disease

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Table I. Characteristics of the included trials and participants.

First author (year)	Design	Follow-up	Age (years) GSH/Control	Participants (males/females) GSH/Control	Intervention Route, dose, frequency	Outcomes	(Refs.)
Hauser (2009)	RCT	4 w	62.6+7.9/ 65.9+12.6	(5/5)/(6/4)	Intravenous push, 1400 mg, Qd	A; B; C; E	(10)
Mischley (2017)	RCT	3 m	60.9+11/ 60.9+11	11; 14/14	Intranasal administration, 300 mg or 600 mg, Qd	A; B; C	(11)
Mischley (2015)	RCT	3 m	-	10; 10/10	Intranasal administration, 300 mg or 600 mg, Qd	A; B; C; E	(12)
Bao (2018)	RCT	4 m	64.6+8.2/ 65.1+9.6	(56/44)/(55/45)	Intravenous drip, 600 mg, Bid	A; B; C; D	(14)
Bao (2003)	RCT	6 w	61.41+9.68/ 58.87+7.94	(14/16)/(16/14)	Intravenous drip, 600 mg, Bid	D	(15)
Hu (2019)	RCT	21 d	66.8+6.9/ 70.7+7	(17/15)/(18/13)	Intravenous drip, 1200-1400 mg, Qd	A; B; C; D; E	(16)
Zhang (2005)	RCT	4 m	56+4.5/ 57+4.9	(12/7)/(11/8)	Intravenous drip, 600 mg, Bid	D	(17)

GSH, reduced glutathione; RCT, randomized controlled trial; Bid, bis in die; Qd, quaque die; w, weeks; m, months; d, days; UPDRS, Unified Parkinson's Disease Rating Scale; A, UPDRS I; B, UPDRS II; C, UPDRS III; D, glutathione peroxidase; E, adverse events; m, months; w, weeks.

In addition, several studies (10,12,16) have reported data surrounding gastrointestinal reactions, dizziness or headache, involuntary movement, labored breathing, strep throat and/or insomnia. The pooled results of these studies revealed that the therapeutic dose of GSH is safe. Further patient studies also indicated that when GSH was repeatedly administered at doses of up to 5 g per day, both orally or intravenously, no toxicity was observed (29,30).

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EFFICACY EVALUATION

CYSTIC FIBROSIS (CF)

Bishop 2005

- 19 subjects aged 6-19 years old
- Randomized, double-blind, placebo-controlled, parallel design
- 10 patients: Glutathione 66 mg/kg/d, divided into four inhalations, for 8 weeks
  - 8 completed study
- 9 patients: placebo (quinine added to mimic odor of GSH)
  - 6 completed study

A Pilot Study of the Effect of Inhaled Buffered Reduced Glutathione on the Clinical Status of Patients With Cystic Fibrosis*

Clark Bishop, MD, FCCP; Valerie M. Hudson, PhD; Sterling C. Hilton, PhD; Cathleen Wilde, BS

Table 3—*Type of Adverse Events During Trial for Each Treatment Group**

Events	Placebo (n = 9)	GSH (n = 10)
Hospitalization for nonacute pulmonary exacerbations	2	1
Rhinitis/sinusitis	3	2
Cough	3	4
Pharyngitis	4	4
Stomach pain/cramps	4	1
Headache	2	4
Chest tightness/bronchospasm	3	1
Nose bleed	3	2
Shortness of breath	2	1

*Data are presented as No. of patients.

Bishop 2005 - Discussion

- "Small airway function improved in the GSH group, as seen in the significant improvement in peak flows and the tendency toward significance of $FEF_{25–75}$ in the ancillary compliance analysis.
  - Because two subjects in the GSH group did not record peak flow data, the peak flow comparison is comparable to the compliance analysis.
- "While the effect size in peak flow is relatively small (40.2 L/m), improvement in small airway function is noteworthy because research[41] in CF pathophysiology suggests that changes in peripheral air flow precede changes in FEV_1 and FVC in this disease."
- "In addition to small airway function, two self-reported secondary indicators significantly improved in the GSH treatment group: subjective sense of improvement ($p = 0.004$), and subjective assessment of cough frequency in the ancillary compliance analysis ($p = 0.03$). A measure of subjective general wellness tended toward significant improvement as well ($p = 0.09$).
- "Finally, none of the outcomes significantly favored the control group over the GSH group."

FEF_{25-75}: forced mid-expiratory flow
FEV_1: forced expiratory volume in one second
FVC: forced vital capacity

Day 2005

- Bryan J. Day, PhD, Associate Professor of Medicine & Pharmaceutical Sciences, National Jewish Medical & Research Center, Denver, CO
- Evaluates studies by Roum (1999), Griese (2004), and Bishop (2005)

with cystic fibrosis. The study by Bishop et al used a higher glutathione dosage (66 mg/kg/d, divided into four inhalations, for 8 weeks). This regimen was also well tolerated and associated with an improvement in peak flow over placebo group, along with a trend toward improvement in a number of other clinical indicators. Given the small size of the trial and the mild airway dysfunction in the cystic fibrosis population studied, these results are encouraging that inhaled glutathione therapy could be beneficial. In summary, inhaled glutathione therapy was well tolerated and efficacious in improving a variety of clinical indicators in all three studies[16–18] reported.

With three small clinical trials[16–18] with positive findings now published, it seems clear that the next logical step is a large multicenter clinical trial. Several obstacles remain to be overcome. These include the cost of safety studies, agreement on dosages, primary indicators, and support from the pharmaceutical industry for an orphan indication. Given that a number of inflammatory lung diseases share a diminished level of glutathione in the epithelial lining fluid and excessive lung inflammatory responses, a glutathione therapeutic may have broader implications than cystic fibrosis. Glutathione may indeed be a radical approach to treat a number of inflammatory lung diseases.

Brian J. Day, PhD
Denver, CO

FDA evaluation: Bishop 2013, Griese 2013

Bishop et al. (2013 abstract; NCT02029521) in an age-stratified, randomized, placebo-controlled, double-blinded, clinical trial, 44 pediatric CF patients were treated with oral reduced L-glutathione for six months (65 mg/kg, devided into three doses per day). The authors concluded that oral reduced L-glutathione should be considered in pediatric CF patients to improve nutritional status, as well as pulmonary function. The authors also concluded that further study is warranted.

Griese et al. (2013; NCT00506688) was a randomized, double-blind, placebo-controlled, parallel design phase 2b, 6 month treatment duration inhalation study conducted in 153 CF patients aged 8 years and older. Of these, 73 treated with active (inhalations of 646 mg of glutathione-Na powder mixed with 4 mL normal saline every 12 hours via eFlow nebulizer) and 80 treated with placebo (inhalations of 4 mL normal saline every 12 hours via eFlow nebulizer). FEV_1 (absolute values), both as pre-post differences ($p=0.180$) and as area under the curve ($p=0.180$) were the primary efficacy endpoints and were not different between the two groups over the 6 month treatment period.

FDA evaluation: Guidelines

In 2013, the Cystic Fibrosis Foundation and members of the Pulmonary Clinical Practice Guidelines Committee published "Cystic Fibrosis Pulmonary Guidelines: Chronic Medication for Maintenance of Lung Health." One study of glutathione (randomized controlled trial by Bishop 2005) and two studies of N-acetylcysteine for patients with CF were reviewed. Based upon this review, the recommendations were unchanged from previous guidelines, i.e., "For individuals with CF, 6 years of age and older, the CF Foundation concludes that the evidence is insufficient to recommend for or against the chronic use of inhaled or oral *N*-acetylcysteine or inhaled glutathione to improve lung function and quality of life or reduce exacerbations" (Mogayzel et al. 2013).

FDA evaluation: Calabrese 2015

Several studies were found in addition to those identified in the Cochrane reviews. In a randomized, single-blind, placebo-controlled (inhaled sodium chloride solution 0.9%), 12 month treatment duration trial conducted in 54 adults and 51 pediatric patients (aged 6-45 years) with CF with 97 completing the trial, inhaled glutathione did not achieve the primary outcome measure of 15% improvement of FEV_1%. The glutathione was administered according to body weight (10 mg/kg) twice daily. The authors noted that most enrolled children had a normal spirometry at baseline with no room of improvement (Calabrese et al. 2015; NCT01450267).

Calabrese 2015

FEV_1 still represents the most important single predictive factor of survival in CF [24,25]. In patients with CF and bacterial chronic infection an annual decline of lung function has been reported [26]. In a recent study, an age-dependent annual decline in percentage predicted FEV_1 was assumed to be between 1% and 3% [27]. We confirmed these data, showing a significant decrease in FEV_1 in the adult placebo group during the study period that did not occur in the GSH group. A decline of functional parameters in the placebo group, although not significant, was also observed by Griese [14].

thus reducing its therapeutic effects in children. Moreover, as inclusion criteria no upper limit was defined for FEV_1 value, so that most enrolled children had a normal spirometry with no room of improvement. As a proof of this, when we mixed the results of adult and children sharing a FEV_1% below 81%, we confirmed a significant improvement of the FEV_1 expressed both as liter and percentage in the GSH arm compared to the placebo. Nevertheless, pediatric patients that assumed GSH showed a significant improvement of the distance walked in 6 min that is considered a marker of disease-severity according to previous data [28].

Based on the results of this clinical trial, the treatment with inhaled GSH is assumed to lead an almost immediate improvement in the FEV_1 in patients with moderate lung disease, a stabilization of BMI in adult population and an improvement of 6MWT in children. In a prospective observational study that is currently ongoing in our center we have selected Lung Clearance Index [29] as a more sensitive alternative to spirometry for detecting efficacy of GSH therapy also in patients with CF and mild lung disease.

Registration number is NCT01450267.

The full trial protocol can be accessed at www.clinicaltrials.gov.

The study has been supported by AIFA.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2014.09.014.

BMI: body mass index
6MWT: 6 minute walking test
AIFA: Agenzia Italiana del Farmaco

FDA evaluation, Visca 2015

In a double-blind, randomized, placebo-controlled, parallel design, 6 month treatment duration, oral reduced glutathione study conducted in 47 pediatric CF patients aged 18 months to 10 years, 24 were treated with active (oral reduced glutathione 65 mg/kg, divided into 3 doses/day) and 23 were treated with placebo (Visca et al. 2015). There were four primary outcomes (change in weight percentile, body mass index (BMI) percentile, height percentile and fecal calprotectin) and four secondary outcomes (white blood cell count, alanine transaminase, vitamin E level and C-reactive protein).[25] In addition, the study showed a significant improvement in FEV_1 expressed as percent and in forced vital capacity (FVC) after six months from the treatment start, mean difference 17.40 (95% confidence interval [CI] 13.69 to 21.11) and 14.80 (95% CI 9.66 to 19.94) respectively.[26] In this study, the supplementation had a positive effect on the nutritional status (BMI %) of the patients, mean difference 17.20 (95% CI 12.17 to 22.23).

The glutathione treatment group gained over six months an average of 0.67 standard deviation (SD) in weight-for-age-and sex z score (wfaszs), equal to 19.1 weight percentile points. The placebo group increased significantly less, 0.1 SD in wfaszs (2.1 weight percentile points), $p<0.0001$. Other changes included:

- Fecal calprotectin improved more in the active treatment group (glutathione 52.0 vs placebo 0.5), $p<0.0001$.
- BMI for glutathione improved 0.69 SD BMI-adjusted-for-age-and-sex z score versus placebo 0.22 SD (BMI percentile 21.7 glutathione vs 5.2 placebo), $p<0.0001$.
- Height increased 0.2 SD in height-for-age-and-sex z score (hfaszs) glutathione versus 0.06 SD hfaszs placebo (height percentile 7.0 glutathione vs 2.6 placebo), $p<0.0001$.

It should be noted that there was an unequal distribution of delF508 homozygote subjects (13.6% of glutathione group versus 27.7% of placebo group) which is concerning because delF508 homozygotes usually have a more severe disease than CF patients with other genetic backgrounds. The small sample size is another potential bias.

Visca 2015

- 47 patients
  - 24 = glutathione 65mg/kg

    divided as 3 doses/day
  - 23 = placebo

Treatment Effects

Both treatment and placebo were well tolerated, and no compliance issues surfaced. On the basis of the repeated-measures mixed-model analyses, patients in the GSH group showed significantly improved results ($P < 0.0001$) on a repeated-measures analysis of variance compared with the placebo group on all 4 primary outcome measures (Table 2).

Adverse Effects

Although 1 patient in the placebo group chose to discontinue the study shortly after it began because of a pulmonary exacerbation requiring hospitalization, no other adverse events were noted in either the treatment or the placebo groups. Bacterial cultures were obtained from swab or sputum at the 3 time points; patients in the treatment group showed no worsening in the pathogenicity or number of bacterial species cultured. Full results on bacterial cultures are available at clinicaltrials.gov and also at the link *http://uvicf.org/researchnewsite/glutathionenewsite/ViscaTrial_Data_and_SupplementaryMaterial.html*.

No patient in the GSH group worsened on any of 11 subjective measures of GI symptoms during the course of the trial, according to the self-reported qualitative symptomatology assessment performed by each patient/parent, and there was a statistically significant trend toward the improvement in these symptoms in the GSH group over time compared with the placebo group, except for ''nausea, heart burn, and <2 bowel movements per week'' (Table 4).

FDA evaluation

b. Severity

CF is a serious or life-threatening disease.

c. Alternative Therapies

Alternative therapies approved for the treatment of CF include bronchodilators such as albuterol and levabuterol; mucus thinners, hypertonic saline and dornase alfa; transmembrane conductance regulator modulator therapies such as ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor; and antibiotics such as azithromycin, tobramycin and aztreonam.

Albuterol and levalbuterol

- https://cysticfibrosisnewstoday.com/bronchodilators-for-cf-albuterol-ventolin-proventil/#:~:text=Albuterol%20is%20a%20bronchodilator%20approved,with%20cystic%20fibrosis%20(CF).

Albuterol is a **bronchodilator approved** by the U.S. Food and Drug Administration (FDA) to treat **bronchospasm** (a narrowing of the airways) in children and adults. Albuterol is available by prescription and may be prescribed to treat coughing and shortness of breath in patients with **cystic fibrosis (CF)**. However, it **does not treat** CF and is used only to ease breathing problems in combination with other medications.

Drugs Indicated to Treat Cystic Fibrosis

Trikafta - $311,503/patient/year

Details on the drug

Vertex Pharmaceuticals' Trikafta is a combination of elexacaftor, ivacaftor, and tezacaftor. The drug is approved to treat patients 12 and older who have at least one F508del genetic mutation, which is estimated to affect about 90% of the CF population, or about 27,000 people in the United States, according to FDA.

Trikafta was shown to be effective in two clinical trials. The first was a 24-week, randomized, double-blind, placebo-controlled trial in 403 patients with an F508del mutation. The second was a four-week, randomized, double-blind, active-controlled trial in 107 patients with two identical F508del mutations.

In the trials, Trikafta was shown to improve lung function by about 14% compared to about a 3% improvement in patients treated with Orkambi, a double-combination CF treatment currently available.

Trikafta will cost $311,503 annually, or $23,896 per 28-day pack, according to the **Securities and Exchange Commission**. Analysts expect the drug to make $630 million in 2020, *Reuters* reports.

Kalydeco - $300,000/patient/year and Orkambi - $259,000/patient/year

Healthc Policy. 2019 Aug; 15(1): 70–80
doi: 10.12927/hcpol.2019.25937
PMCID: PMC7008693
PMID: 31629457
Language: English | French

Orphan Drug Pricing and Costs: A Case Study of Kalydeco and Orkambi

Aidan Hollis, PhD

Ivacaftor (Kalydeco) is indicated for the treatment of CF in patients with certain genetic mutations. Only 2,600 patients globally had the specific genetic mutation that made them eligible for the first approved indication of ivacaftor (Vertex Pharmaceuticals Incorporated 2012). In response, Vertex, the manufacturer, priced Kalydeco in the US at about $300,000 per patient per year of treatment following its Food and Drug Administration (FDA) approval in 2012 (Silverman 2017). Starting in 2016, Vertex marketed a combination product (Orkambi) consisting of ivacaftor and lumacaftor, designed to address a more common mutation. Vertex now indicates that its addressable population globally is over 25,000 patients, which massively increases Vertex's potential revenues (Leiden 2015). Orkambi is priced in the US at $259,000 per patient per year (Weisman 2015). The pricing of these medications has been challenging for insurers (Grant 2017; O'Sullivan et al. 2013; Senior 2015).

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7008693/

Source: https://www.advisory.com/daily-briefing/2019/10/28/cf-drug#:~:text=Trikafta%20will%20cost%20%24311%2C503%20annually,million%20in%202020%2C%20Reuters%20reports.

Safety Profile of CF Therapies

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRIKAFTA safely and effectively. See full prescribing information for TRIKAFTA.

TRIKAFTA® (elexacaftor, tezacaftor, and ivacaftor tablets; ivacaftor tablets), co-packaged for oral use
Initial U.S. Approval: 2019

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	06/2021
Dosage and Administration (2)	06/2021
Warnings and Precautions (5.1)	10/2021

----------INDICATIONS AND USAGE----------

TRIKAFTA is a combination of ivacaftor, a CFTR potentiator, tezacaftor, and elexacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on *in vitro* data.
If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one *F508del* mutation or a mutation that is responsive based on *in vitro* data. (1)

----------DOSAGE AND ADMINISTRATION----------

Recommended Dosage for Adult and Pediatric Patients aged 6 Years and Older

Age	Morning Dose	Evening Dose
6 to less than 12 years weighing less than 30 kgs	Two tablets, each containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg	One tablet of ivacaftor 75 mg
6 to less than 12 years weighing 30 kgs or more	Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	One tablet of ivacaftor 150 mg
12 years and older	Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	One tablet of ivacaftor 150 mg

- TRIKAFTA should be taken with fat-containing food. (2.1, 12.3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Elevated transaminases and hepatic injury: Liver failure leading to transplantation has been reported in a patient with cirrhosis and portal hypertension while receiving TRIKAFTA. Avoid use of TRIKAFTA in patients with pre-existing advanced liver disease, (e.g., as evidenced by cirrhosis, portal hypertension, ascites, hepatic encephalopathy) unless the benefits are expected to outweigh the risks. If used in these patients, they should be closely monitored after the initiation of treatment. Isolated elevations of transaminases or bilirubin have been observed in CF patients treated with TRIKAFTA. In some instances, transaminase elevations have been associated with concomitant elevations in total bilirubin and/or international normalized ratio (INR) and have resulted in patients being hospitalized for intervention, including patients without a history of pre-existing liver disease. Monitor liver function tests (ALT, AST, and bilirubin). Interrupt dosing in the event of significant elevations. In patients with a history of hepatobiliary disease or liver function test elevations, monitor more frequently. (2.3, 5.1, 8.7)
- Use with CYP3A inducers: Concomitant use with strong CYP3A inducers (e.g., rifampin, St. John's wort) significantly decrease ivacaftor exposure and are expected to decrease elexacaftor and tezacaftor exposure, which may reduce TRIKAFTA efficacy. Therefore, co-administration is not recommended. (5.2, 7.1, 12.3)
- Cataracts: Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor-containing regimens. Baseline and follow-up examinations are recommended in pediatric patients initiating TRIKAFTA treatment. (5.4, 8.4)

----------ADVERSE REACTIONS----------

The most common adverse drug reactions to TRIKAFTA (≥5% of patients and at a frequency higher than placebo by ≥1%) were headache, upper respiratory tract infection, abdominal pain, diarrhea, rash, alanine aminotransferase increased, nasal congestion, blood creatine phosphokinase increased, aspartate aminotransferase increased, rhinorrhea, rhinitis, influenza, sinusitis and blood bilirubin increased. (6.1)

Source: https://pi.vrtx.com/files/uspi_elexacaftor_tezacaftor_ivacaftor.pdf

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ORKAMBI safely and effectively. See full prescribing information for ORKAMBI.

ORKAMBI® (lumacaftor/ivacaftor) tablets, for oral use
caftor) oral granules

T MAJOR CHANGES----------

8/2018
8/2018

ATIONS AND USAGE----------

f lumacaftor and ivacaftor, a cystic fibrosis
gulator (CFTR) potentiator, indicated for the
) in patients age 2 years and older who are
utation in the *CFTR* gene. If the patient's
-cleared CF mutation test should be used to detect
utation on both alleles of the *CFTR* gene. (1)

KAMBI have not been established in patients
zygous for the *F508del* mutation. (1)

AND ADMINISTRATION----------

rough 5 years and weighing less than 14 kg: one
containing lumacaftor 100 mg/ivacaftor 125 mg)
mL) of soft food or liquid and administered
h fat-containing food. (2.1, 12.3)
rough 5 years and weighing 14 kg or greater:
ach containing lumacaftor 150 mg/ivacaftor
spoon (5 mL) of soft food or liquid and
12 hours with fat-containing food. (2.1, 12.3)
rough 11 years: two tablets (each containing
ftor 125 mg) taken orally every 12 hours with
12.3)
nts age 12 years and older: two tablets (each
0 mg/ivacaftor 125 mg) taken orally every
ng food. (2.1, 12.3)
vith moderate or severe hepatic impairment. (2.2,

BI in patients taking strong CYP3A inhibitors,
or the first week of treatment. (2.3, 7.1, 12.3)

ORMS AND STRENGTHS----------

----------WARNINGS AND PRECAUTIONS----------

- Use in patients with advanced liver disease: ORKAMBI should be used with caution in these patients and only if the benefits are expected to outweigh the risks. If ORKAMBI is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced. Liver function decompensation, including liver failure leading to death, has been reported in CF patients with pre-existing cirrhosis with portal hypertension. (2.2, 5.1, 6.1)
- Liver-related events: Elevated transaminases (ALT/AST) have been observed in some cases associated with elevated bilirubin. Measure serum transaminases and bilirubin before initiating ORKAMBI, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Interrupt dosing in patients with ALT or AST >5 x upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN. Following resolution, consider the benefits and risks of resuming dosing. (5.2, 6.1)
- Respiratory events: Chest discomfort, dyspnea, and respiration abnormal were observed more commonly during initiation of ORKAMBI. Clinical experience in patients with percent predicted FEV_1 ($ppFEV_1$) <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy. (5.3, 6.1)
- Blood pressure: Increased blood pressure has been observed in some patients. Periodically monitor blood pressure in all patients. (5.4, 6.1)
- Drug interactions: Use with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index may decrease systemic exposure of the medicinal products and co-administration is not recommended. Hormonal contraceptives should not be relied upon as an effective method of contraception and their use is associated with increased menstruation-related adverse reactions. Use with strong CYP3A inducers may diminish exposure of ivacaftor, which may diminish its effectiveness; therefore, co-administration is not recommended. (5.5, 6.1, 7, 12.3)
- Cataracts: Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ORKAMBI and ivacaftor, a component of ORKAMBI. Baseline and follow-up examinations are recommended in pediatric patients initiating ORKAMBI. (5.6)

----------ADVERSE REACTIONS----------

The most common adverse reactions to ORKAMBI (occurring in ≥5% of patients with CF homozygous for the *F508del* mutation in the *CFTR* gene) were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, blood creatine phosphokinase increased, rash, flatulence, rhinorrhea, influenza. (6.1)

Source: https://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf

FDA evaluation

d. Conclusion

There is conflicting evidence regarding the clinical effectiveness of antioxidant supplementation including glutathione in CF. Based on the available evidence, glutathione (administered either orally or by inhalation) appears to improve lung function in some cases and decrease oxidative stress; however, due to the very intensive antibiotic treatment and other treatments that CF patients receive, the beneficial effect of glutathione is very difficult to assess in patients with chronic infection without a very large population sample and a long-term (at least six months) study period. There is insufficient information to support the effectiveness of glutathione for the treatment of CF. The existence of approved drugs to treat the disease weigh against including glutathione on the list, particularly in light of CF being a serious or life-threatening disease.

Trial design, benefits, cost

- Day 2005

With three small clinical trials[16–18] with positive findings now published, it seems clear that the next logical step is a large multicenter clinical trial. Several obstacles remain to be overcome. These include the cost of safety studies, agreement on dosages, primary indicators, and support from the pharmaceutical industry for an orphan indication. Given that a number of inflammatory lung diseases share a diminished level of glutathione in the epithelial lining fluid and excessive lung inflammatory responses, a glutathione therapeutic may have broader implications than cystic fibrosis. Glutathione may indeed be a radical approach to treat a number of inflammatory lung diseases.

Brian J. Day, PhD
Denver, CO

- Advisory.com article

Trikafta was shown to be effective in two clinical trials. The first was a 24-week, randomized, double-blind, placebo-controlled trial in 403 patients with an F508del mutation. The second was a four-week, randomized, double-blind, active-controlled trial in 107 patients with two identical F508del mutations.

In the trials, Trikafta was shown to improve lung function by about 14% compared to about a 3% improvement in patients treated with Orkambi, a double-combination CF treatment currently available.

Trikafta will cost $311,503 annually, or $23,896 per 28-day pack, according to the **Securities and Exchange Commission**. Analysts expect the drug to make $630 million in 2020, *Reuters* reports.

Cystic Fibrosis Conclusion

- Overwhelming majority of data suggests inhaled, IV, and oral glutathione is safe at doses up to 600mg/day or 65mg/kg/day
- 7 clinical trials for cystic fibrosis, involving 280 patients
- Efficacy data supports GSH utilization
  - Suggests positive subjective outcomes
  - Majority of studies show positive objective outcomes
  - No studies showed inferiority to placebo
- No studies report serious adverse events in treatment groups

Cystic Fibrosis Clinical Trials

Author Year	n	Study Design	Clinical Outcome	Adverse Events
Bishop 2005	10	DBPCRT	Significant improvement for GSH arm	None
Roum 1999	7	Prospective	Improvement with GSH treatment	None
Griese 2004	17	Prospective	FEV1 improved after 14 days	None
Bishop 2013	44	DBPCRT	Oral GSH improves pediatric CF patients	None
Griese 2013	73	DBPCRT	No difference between GSH and placebo	AE's and dropouts were more numerous in placebo arm
Calabrese 2015	105	DBPCRT	Improvements when measured correctly	None
Visca 2015	24	DBPCRT	Oral GSH improves outcomes on several important measures	None
7 clinical trials	280			

DBPCRT = double-blind placebo-controlled randomized trial

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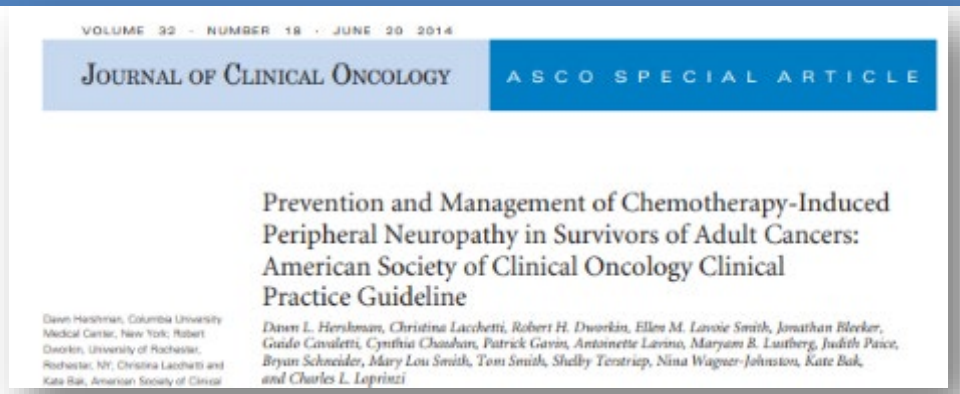
EFFICACY EVALUATION

REDUCTION OF THE SIDE EFFECTS OF CHEMOTHERAPY

ASCO 2014 Statement


VOLUME 32 · NUMBER 19 · JUNE 20 2014
JOURNAL OF CLINICAL ONCOLOGY
ASCO SPECIAL ARTICLE

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline

Dawn L. Hershman, Christina Lacchetti, Robert H. Dworkin, Ellen M. Lavoie Smith, Jonathan Bleeker, Guido Cavaletti, Cynthia Chauhan, Patrick Gavin, Antoinette Lavino, Maryam B. Lustberg, Judith Paice, Bryan Schneider, Mary Lou Smith, Tom Smith, Shelby Terstriep, Nina Wagner-Johnston, Kate Bak, and Charles L. Loprinzi

Six small randomized trials[25,26,47-50] evaluated the protective effects of glutathione (GSH) against platinum-based neurotoxicity. Five of these trials[25,47-50] reported a statistically significant reduction in neurotoxicity, in one form or another, with administration of GSH compared with placebo. Benefits included a reduction in incidence and severity of neuropathy and improvements in nerve conduction and QOL. In addition, a small, randomized, placebo-controlled pilot study of *N*-acetylcysteine, an antioxidant known to increase serum glutathione concentrations, was conducted in 14 patients with stage III colon cancer receiving oxaliplatin-based adjuvant chemotherapy.[23] This study reported that grade 2 to 4 sensory neuropathy was lower in the treatment arm (20%) compared with the placebo arm (73%) after 12 cycles of chemotherapy ($P < .05$). In contrast to the above data suggesting that GSH is beneficial, a recent larger placebo-controlled trial was unable to provide data supporting the benefit of GSH for the prevention of neurotoxicity in 185 patients receiving paclitaxel/carboplatin therapy.[51] As carboplatin is the least neurotoxic of the platinum agents, it appears that most of the neuropathy from this regimen was dictated by paclitaxel. Thus, the results of this study suggest that GSH is not an effective agent in the prevention of taxane-induced CIPN. It

QOL: quality of life
CIPN: chemotherapy-induced peripheraly neuropathy

Cozzaglio 1990

disappointing results are not the consequence of interference of GSH on the cytotoxic efficacy of cisplatin. The lack of incidence of severe toxicity of this regimen supports the role of reduced glutathione as a potential protective against cisplatin nephrotoxicity. Although these preliminary results suggest that further studies with the present regimen in this disease are not warranted, in view of its safety this program deserves evaluation in the treatment of neoplastic diseases responsive to 5-fluorouracil/cisplatin.

Tumori. 1990 Dec 31;76(6):590-4.

A feasibility study of high-dose cisplatin and 5-fluorouracil with glutathione protection in the treatment of advanced colorectal cancer

L Cozzaglio [1], R Doci, G Colella, F Zunino, G Casciarri, L Gennari

Affiliations + expand

PMID: 2284698

Erratum in

Tumori 1991 Feb 28;77(1):following 93. Colla G [corrected to Colella G]

Abstract

On the basis of previous studies supporting that glutathione (GSH) reduced cisplatin nephrotoxicity we have designed a new regimen in the treatment of advanced colorectal cancer, which included GSH as a modulator of cisplatin-induced toxicity. Eleven untreated patients with measurable metastatic colorectal cancer received 5-fluorouracil (750 mg/m2, daily continuous infusion for days 1-5) and cisplatin (40 mg/m2 1 hour-infusion for days 6-8) given every 4 weeks. Reduced glutathione (2.5 g) was delivered i.v. prior to each cisplatin infusion. Toxicity was minimal and reversible and included nausea/vomiting (11 cases), mild neurotoxicity (4 cases) and leukopenia (2 cases); only 2 patients showed moderate and transient increases of serum creatinine (less than 2 mg/dl) and BUN. Renal function impairment was also monitored by magnesemia levels and urinary marker enzymes indicating minimal cumulative nephrotoxicity. Out of 10 evaluable patients, only 2 partial responses were observed. The median survival was 9 months (range 5-26). The study was closed, since the preliminary results do not suggest any therapeutic advantage in adding cisplatin to 5-fluorouracil in the present schedule, even using an intensive regimen. Indirect evidence suggests that these disappointing results are not the consequence of interference of GSH on the cytotoxic efficacy of cisplatin. The lack of incidence of severe toxicity of this regimen supports the role of reduced glutathione as a potential protective against cisplatin nephrotoxicity. Although these preliminary results suggest that further studies with the present regimen in this disease are not warranted, in view of its safety this program deserves evaluation in the treatment of neoplastic diseases responsive to 5-fluorouracil/cisplatin.

Di Re 1993

for the 79 analyzed cases was 40 months. The toxicity of the regimen was moderate. Nausea/vomiting was the most severe acute toxicity. Myelotoxicity was acceptable, with severe leukopenia and thrombocytopenia (grade 4) occurring in 8% and 3% of patients, respectively. Nephrotoxicity was minimal with a transient increase (to <2 mg/dL) in serum creatinine in only 6 patients (8%). Peripheral neurotoxicity and ototoxicity were the most significant long-term toxicities. The severity of these side effects (grade 3 WHO neurotoxicity occurred in only 4% of patients) was apparently less than has been reported with other high-dose cisplatin regimens. Neurotoxicity required discontinuation of therapy in three patients after four courses. Most affected patients had complete or partial recovery of symptoms with time.

Discussion: The efficacy and tolerability of the regimen confirm the feasibility of this new approach including glutathione in order to increase cisplatin dose intensity. The superiority of this regimen over standard induction therapy should be confirmed in randomized trials.

WHO: World Health Organization

Bohm 1999

toxicity was moderate with lack of significant nephrotoxicity. Neurotoxicity and ototoxicity were acceptable and in no patient was treatment discontinued for those toxic effects. Myelotoxicity was somewhat more severe than that observed with our previous study with high-dose cisplatin and probably related to the addition of carboplatin. Of the 40 responsive patients, 23 (46%) had a pathological complete response and 4 (8%) had a clinical complete response (without second-look laparotomy). The efficacy of the present protocol was also documented by overall survival (median survival >48 months), which appeared to be better than expected with the current therapy in this group with advanced/bulky disease. The impressive efficacy suggests a possible contribution of reduced glutathione itself in improving the outcome, as supported by preclinical studies. The results of this study should be placed in context with current platinum-based therapy including paclitaxel.

Clinical Study

ONCOLOGY

Oncology 1999;57:115–120

Dose Intensification of Platinum Compounds with Glutathione Protection as Induction Chemotherapy for Advanced Ovarian Carcinoma

Silvia Böhm Saro Oriana Gianbattista Spatti Francesco Di Re Gianluigi Breasciani Carlo Pirovano Ilaria Grosso Cinzia Martini Augusto Caraceni Silvana Pilotti Franco Zunino

Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italia

Leal 2014

- Glutathione did not interfere with any chemotherapeutic regimen

Effect of glutathione on cancer outcome

There were no significant differences between the two study arms with regards to the time to disease progression in the gynecologic patients per CA-125-determined disease progression, defined as an elevation of greater than two times the upper limit of normal on two occasions, separated by at least one week, when the CA-125 level had normalized during, or upon completion of therapy.

Evaluation of glutathione toxicity

There were no statistically significant or clinically apparent toxicity differences between the two study arms with regard to multiple evaluated toxicities (including fatigue, nausea, vomiting, diarrhea, rash, anaphylaxis, anemia and leukopenia).

CA-125: cancer antigen 125

Leal 2014 (continued)

Discussion

The negative findings from this current trial contrast with the positive pilot findings[10–17] that led to its development. Of the data available to investigate the efficacy of glutathione as a CIPN preventative agent, most of the studies have been conducted in patients receiving either oxaliplatin- or cisplatin-based therapy. In comparing the neurotoxicity of the agents involved in the current trial, carboplatin is the least neurotoxic of the platinum agents and is less neurotoxic than paclitaxel. While the results of this current study support that glutathione is not an effective agent in the prevention of taxane-induced CIPN when given in combination with carboplatin, the current results may not be applicable for cisplatin- or oxaliplatin-induced neurotoxicity.

A recently published study by Smith et al.[26] supports that therapies for chemotherapy-induced neuropathy may be different for different chemotherapy agents. Their manuscript reported data from a randomized, double-blind, placebo-controlled, crossover trial to investigate the efficacy of duloxetine for the treatment of established CIPN among a cohort of patients with either taxane- or oxaliplatin-induced CIPN. These authors found a significant decrease in patient-reported average pain among those that received duloxetine, compared to placebo. However, in a subgroup analysis, it appeared that duloxetine was efficacious in patients with oxaliplatin-induced CIPN but not efficacious in those with taxane-induced CIPN. This may explain the differences between the findings from the present study and what has been previously suggested in other pilot trials looking at oxaliplatin- or cisplatin-based therapies.

FDA evaluation, pg 38

A total of 35 ovarian carcinoma patients received IV cisplatin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks. Glutathione 5 g in 200 mL normal saline was intravenously administered to all patients prior to cisplatin to potentially provide chemoprotection from cisplatin adverse effects. The hydration protocol was 1000 mL of fluids without diuretics (the authors stated that conventional hydration for safe cisplatin administration was 2000-3000 mL of fluids). Treatment was well tolerated with no nephrotoxic or neurotoxic effects (Bohm et al. 1991).

When 22 patients with advanced head and neck carcinoma were treated with 5-fluorouracil 400 mg/m^2, folinic acid 500 mg/m^2, cisplatin in escalating doses from 20-40 mg/m^2, and glutathione 1.5 g/m^2, the glutathione appeared to be able to reduce, at least partially, cisplatin-related nephrotoxicity permitting the delivery of higher cisplatin doses. Grade 1 renal toxicity was seen in two of the 22 patients at the cisplatin dose of 30 mg /m^2 per week without forced diuresis. Grade 2 renal toxicity was recorded in the first two patients who received cisplatin 40 mg/m^2 per week with severe impairment of planned dose-intensity. Therefore, no further patients were entered at the cisplatin 40 mg/m^2 dose level (Gebbia et al. 1992).

FDA evaluation, pg 38

In a randomized, double-blind, placebo-controlled, 15 week treatment study, 50 patients with advanced gastric cancer were treated with a weekly cisplatin-based regimen. IV glutathione 1.5 g/m^2 in 100 mL normal saline was also administered to 25 of these patients over a 15-minute period immediately before dosing with once weekly cisplatin 360 mg/m^2, in addition to glutathione 600 mg by IM injection on days 2-5, with saline administered (instead of glutathione) to the 25 placebo patients. After 9 weeks, no patient showed clinically evident neuropathy in the glutathione arm, whereas 16 patients in the placebo arm did. After the 15 weeks, 4 of the 24 assessable patients in the glutathione arm suffered from neurotoxicity versus 16 of 18 in the placebo arm (p=0.0001). The response rate was 76% (20% complete response [CR]) in the glutathione group and 52% (12% CR) in the placebo arm (Cascinu et al. 1995).

FDA evaluation, pg 39

Weekly IV glutathione 1.5 grams/m^2 (along with weekly cisplatin 40 mg/m^2, fluorouracil 500 mg/m^2, epi-doxorubicin 35 mg/m^2 and 6S-stereoisomer of leucovorin 250 mg/m^2 and on the other days, filgrastim 5 mg/kg) was administered to 105 patients with advanced gastric cancer to reduce cisplatin-induced neurotoxicity. One cycle consisted of eight 1-week treatments. Patients who showed a response or stable disease received a further 6 weeks of therapy. Mean survival was 11 months, with 2-year survival rate of 5%. Only three subjects complained of neurotoxicity: one WHO grade 1 and two WHO Grade 2 (Cascinu et al. 1997).

Glutathione 2.5 grams was intravenously administered to 50 patients with untreated stage III or IV epithelial ovarian cancer before each cisplatin (40 mg/m^2 once daily on Days 1-4) and carboplatin (160 mg/m^2 once daily on Day 5) administration. Patients also underwent standard IV hydration. The cycle was repeated after 28 days. After 2 courses of induction chemotherapy, the patients underwent surgical reevaluation with debulking, followed by a further 3 cycles of 120 mg/m^2 cisplatin. Toxicity was moderate with lack of significant nephrotoxicity. Neurotoxicity and ototoxicity were acceptable, and no patient discontinued treatment due to toxicity (Bohm et al. 1999).

FDA evaluation, pg 39

A total of 52 patients with advanced colorectal cancer received glutathione 1.5 grams/m^2 or normal saline placebo before each bimonthly dose of oxaliplatin. The dose of oxaliplatin was 400 mg/m^2 for the first four cycles of treatment, then 800 mg/m^2 for the next eight cycles of treatment and then 1200 mg/m^2 for the last 12 cycles of treatment. At the fourth cycle, seven patients showed clinically evident neuropathy in the glutathione arm, whereas 11 patients in the placebo arm did. After the eighth cycle, nine of 21 assessable patients in the glutathione arm suffered from neurotoxicity compared with 15 of 19 in the placebo arm. The neurophysiologic investigations (sural sensory nerve conduction) showed a statistically significant reduction of the values in the placebo arm, but not in the glutathione arm. The response rate was 26.9% in the glutathione arm and 23.1% in the placebo arm, showing no reduction in activity of oxaliplatin (Cascinu et al. 2002).

FDA evaluation, pg 39

A total of 27 patients were randomized to receive glutathione 1.5 grams/m^2 or saline solution before their oxaliplatin/5-flurouracil/leucovorin (FOLFOX) regimen for colorectal cancer. While the glutathione group showed a statistically significant reduction of neurotoxicity (p=0.0037) compared to the placebo arm, the glutathione group also demonstrated a significantly lower (p=0.0356) oxaliplatin PK parameter "total area under the plasma concentration time curve", i.e., median oxaliplatin AUC_{tot} (ng x h/mL) for the Control group was 166,950 ng x h/mL, while it was only 127,260 ng x h/mL for the glutathione group, and a significantly smaller (p=0.0066) apparent steady-state volume of distribution when glutathione was co-administered and the PK results were evaluated for oxaliplatin in ultrafiltered plasma (Milla et al. 2009).

In summary, results of the studies using glutathione for reduction of side effects of chemotherapy are mixed. Some show potential benefit but they are small studies and lack a control arm. The largest placebo-controlled study showed no benefit of glutathione, and one study showed that glutathione significantly lowered the level of a chemotherapeutic agent which may affect efficacy.

Milla 2009 - abstract

proteins. The determination of Pt-DNA adduct formation shows no statistically significant differences between the two arms. In conclusion, this study indicates that coadministration of GSH is an effective strategy to reduce the oxaliplatin-induced neurotoxicity without impairing neither the pharmacokinetics of oxaliplatin, nor the Pt-DNA adduct formation. ***Anti-Cancer Drugs*** 20:396–402 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

PK: pharmacokinetic
Pt: platinum

Milla 2009

- Discussion

The Pt-DNA adducts formation on WBC shows no statistically significant differences between the two experimental arms suggesting that there is no GSH influence on Pt-DNA adducts formation in tumor cells as well. Recently, an association between adduct levels in WBC and tumor response was reported [24], but further studies, designed to validate Pt-DNA adduct formation as a surrogate for antitumor activity during both adjuvant and palliative therapy, are required.

The ability of GSH to prevent the oxaliplatin-induced neurotoxicity without impairing Pt-DNA adduct formation in tumor cells (or in WBC taken as a model), could be explained by the pharmacokinetic properties of this compound. Exogenous GSH infusion, administered intravenously, is rapidly removed from the plasma compartment, but is not taken up by most of the cells (and probably even by the tumor cells) except for those tissues requiring high concentrations of antioxidant species [13]. Thus, high concentrations of GSH are found in the kidney [29] and in the cells strongly exposed to reactive oxygen species such as those of the central and peripheral nervous system [30–32]. This distribution could explain the protective effect of GSH against nephrotoxicity induced by cisplatin and neurotoxicity induced by oxaliplatin.

The lack of toxicity and interference with pharmacokinetics and effects of oxaliplatin suggest that GSH may be a promising drug for the prevention or delay of oxaliplatin-induced neuropathy in colorectal cancer patients.

WBC: white blood cells

FDA evaluation, pg 40

b. Severity

Side (adverse) effects of chemotherapy can be serious or life-threatening.

c. Alternative Therapies

Alternative therapies approved to reduce the side effects of chemotherapy include palifermin injection, amifostine, dexrazoxane, and mesna.

d. Conclusion

Several small studies have been conducted to show glutathione's effects on side effects related to different chemotherapeutic agents for various cancers. Available data are insufficient to support the effectiveness of glutathione for reduction of side effects of chemotherapy. FDA concurs with health professional organizations that there is lack of high-quality and consistent evidence to support the use of certain agents, including glutathione, to prevent chemo-related peripheral neuropathy, and that study results of glutathione to prevent chemo-related peripheral neuropathy have been mixed and more research is needed. In addition, the existence of approved drugs to treat the disease weigh against including glutathione on the list, particularly in light of adverse effects of chemotherapy being serious or life-threatening.

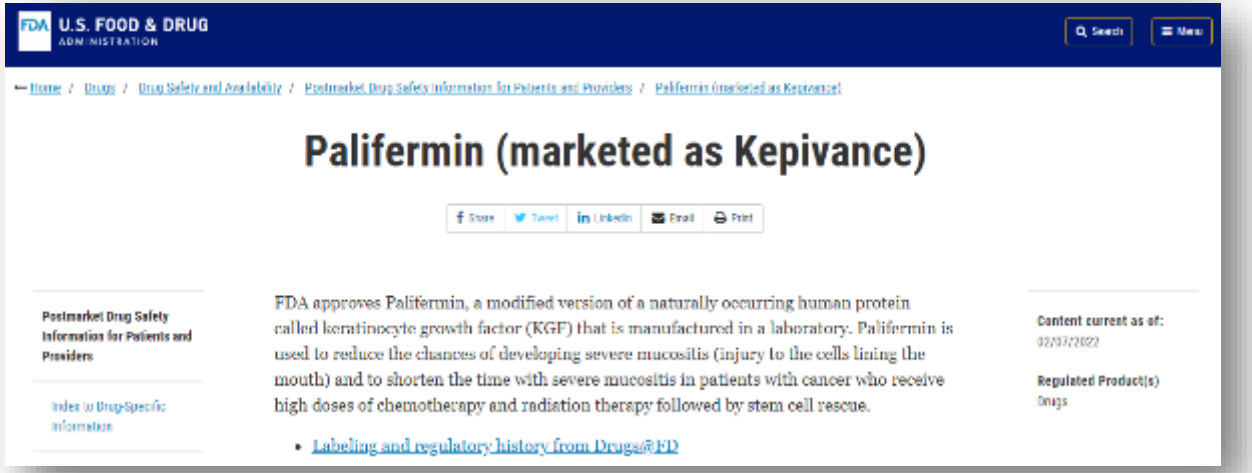
Palifermin is not indicated for neuropathies

- https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125103lbl.pdf

INDICATIONS AND USAGE

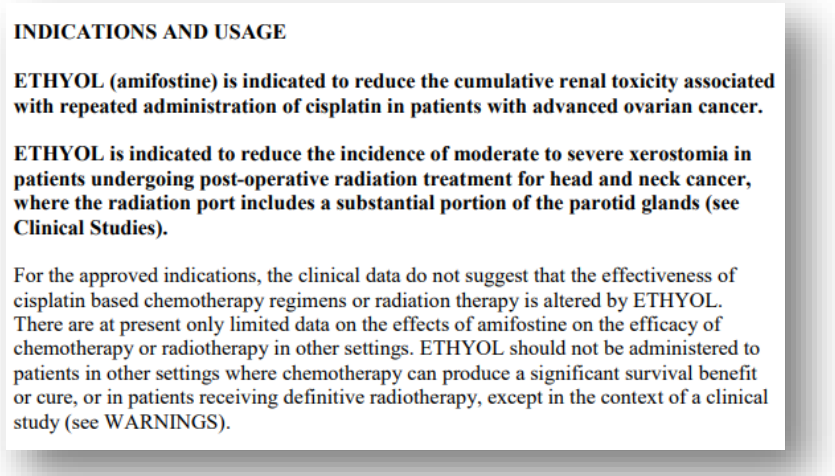
Kepivance™ is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support.

The safety and efficacy of Kepivance™ have not been established in patients with non-hematologic malignancies (see **PRECAUTIONS**).



Dexrazoxane, mesna, amifostine: not indicated for neuropathy

- Dexrazoxane is for anthracycline-induced cardiomyopathy prophylaxis
- MESNEX (mesna) is indicated as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis.
- Amifostine: For nephrotoxicity prophylaxis in patients receiving cisplatin for advanced ovarian cancer
  - NOTE: Amifostine may interfere with the antitumor activity of chemotherapy regimens. DO NOT use in patients receiving chemotherapy for other malignancies in which chemotherapy can produce a significant benefit or cure, except in the context of a clinical study.[49124]



INDICATIONS AND USAGE

ETHYOL (amifostine) is indicated to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer.

ETHYOL is indicated to reduce the incidence of moderate to severe xerostomia in patients undergoing post-operative radiation treatment for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands (see Clinical Studies).

For the approved indications, the clinical data do not suggest that the effectiveness of cisplatin based chemotherapy regimens or radiation therapy is altered by ETHYOL. There are at present only limited data on the effects of amifostine on the efficacy of chemotherapy or radiotherapy in other settings. ETHYOL should not be administered to patients in other settings where chemotherapy can produce a significant survival benefit or cure, or in patients receiving definitive radiotherapy, except in the context of a clinical study (see WARNINGS).

Leal 2014

Despite substantial efforts, there are no recommended agents for preventing chemotherapy-induced neuropathy at this time. A recent large trial illustrated that intravenous calcium/

Package leaflet: Information for the user TAD 600 mg / 4 ml powder and solvent for solution for injection TAD 2500 mg / 25 ml powder and solvent for solution for infusion

Glutathione

Contents of this leaflet:

1.What TAD is and what it is used for

TAD contains glutathione (GSH), a physiological tripeptide composed of glutamic acid, cysteine and glycine which is involved in numerous biological processes and plays an important role in the elimination reactions of toxic substances from the body. Parenterally administered glutathione belongs to the pharmacotherapeutic group of antidotes, substances capable of transforming a toxic agent into a harmless or slightly harmful compound. TAD is used to prevent neuropathy (a disease of the nervous system) following treatment with medicines called chemotherapy, such as cisplatin or similar, used to treat certain types of cancer.

2.What you need to know before you take TAD

Do not take TAD
If you are allergic to glutathione or any of the other ingredients of this medicine.

Warnings and Precautions
Talk to your doctor or nurse before using TAD.

Other medicines and TAD

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

At the recommended doses, TAD does not interfere with the therapeutic activity of the chemotherapeutic agent. In the absence of incompatibility studies, the medicinal product must not be mixed with other products.

Pregnancy and breastfeeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

The available data indicate that glutathione, due to its nature as a substance physiologically present in cells, does not give rise to undesirable effects in pregnant or breastfeeding women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryofoetal development, parturition or postnatal development.

TAD Packge Leaflet (continued)

4.**Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Skin rashes have been reported very rarely after intramuscular administration and disappeared on discontinuation of therapy. Injection site pain has also been reported.
As with all parenteral solutions, febrile reactions, injection site infections, venous thrombosis or phlebitis, extravasal spread may occur.
In the event of an immediate adverse reaction during intravenous infusion, discontinue administration and, where possible, store the non-administered fluid for possible examination.

TAD Package Insert

4.2 Posology and method of administration

Dosage

The generally recommended daily dose of TAD in patients receiving cisplatin or analogue chemotherapy is 1.5 g / m_2(corresponding to 2.5 g) administered by slow intravenous route. However, the dosage is dependent on the age, weight and clinical condition of the patient, and should also be correlated with the dose and dosage regimen of the chemotherapy. In case of administration of glutathione in combination with chemotherapy, the intravenous infusion of TAD should take place within 15 - 30 minutes before the start of chemotherapy. In the event of long-term therapies, lower doses of the product can be used (600 mg) to be administered intramuscularly or slowly intravenously.

CIPN Conclusion

- 932 patients evaluated in published trials from 1990 forward
- 1 study failed to show GSH benefits using different chemo regimen from other studies
  - Author notes no safety issues, no interference with chemo regimen, and provides plausible hypothesis for unexpected results
- 15 studies show no clinically meaningful interaction with chemotherapy
- 15 studies show no clinically meaningful patient safety concerns caused by GSH
- Approved product in Italy, indicated for CIPN
- No FDA-approved products for this serious condition

CIPN Clinical Trials

Author Year	n	Study Design	Clinical Outcome	Interactions with chemotherapy
Bogliun 1992	33	RCT	“Safe & effective”, “extremely low peripheral neurotoxicity”	GSH did not impair CDDP effectiveness
Bogliun 1996	54	RCT	“[GSH]-treated groups at the end of treatment constantly evidenced a trend toward less severe neurotoxicity…”	GSH did not impair CDDP effectiveness
Colombo 1995	33	RCT, phase II	“neuroprotection was detected in the GSH treated group, and no major difference was observed in terms of other toxicities between the groups.”	None noted; 56% of GSH-treated patients were able to tolerate 100% CDDP dose vs. 27% in control arm
Cascinu 1995	50	DBPCRT	Significant protection in GSH arm (0 vs. 16 experiencing neuropathy at 9 weeks; 4 of 24 vs. 16/18 at 15 weeks)	GSH group had 76% patient response rate, 20% CR to CDDP; placebo had 52% (12% CR)
Cascinu 1997	105	Phase II multicenter	Only three patients complained of neurotoxicity: One WHO grade I; two WHO grade II	None
Cascinu 2002	52	DBPCRT	11 patients in placebo arm experienced neuropathy vs. only 2 in GSH arm. Placebo arm had significant reduction in sensory nerve conduction	Response rate was similar, showing no reduction in oxaliplatin effectiveness

DBPCRT: double-blind placebo-controlled randomized trial
PCRT: placebo-controlled randomized trial
RCT: randomized controlled trial
CR: complete response
CDDP: cisplatin

CIPN Clinical Trials

Author Year	n	Study Design	Clinical Outcome	Interactions with chemotherapy
Smyth 1997	151	DBPCRT	58% of GSH patients received full 6-courses of CDDP at any dose vs. 39% placebo (p=0.04). “The results demonstrate that adding GSH to CDDP allows more cycles of CDDP treatment to be administered because less toxicity is observed and the patient's quality of life is improved.”	“It appears GSH:CDDP ratio of 30:1 allows good protection without interfering with therapeutic activity.”
Cozzaglio 1990	11	Prospective	“The lack of incidence of severe toxicity of this regimen supports the role of reduced glutathione as a potential protective against cisplatin nephrotoxicity.”	None interference from GSH was identified; focus was benefits of adding CDDP + 5-fluorouracil
Leal 2014	185	DBPCRT, phase III	No difference between placebo and GSH + carboplatin. GSH may not be effective with *carboplatin-induced* neurotoxicity	No significant differences with regard to time to disease progression
Bohm 1991	35	Prospective	“The treatment was well tolerated; no nephrotoxic or neurotoxic manifestations were observed.”	“Taken together with previous observations, these results support the view that the use of GSH is a successful approach in the attempt to optimize cisplatin treatment, providing a new modality of drug administration for out-patient treatment.”
Gebbia 1992	22	Prospective	“Reduced glutathione seems to be able to reduce, at least partially, CDDP-related nephrotoxicity permitting the delivery of higher CDDP doses.“	“In conclusion, the schedule seems effective and may be safely given to patients with advanced head and neck cancer on outpatient basis.”

CIPN Clinical Trials

Author Year	n	Study Design	Clinical Outcome	Interactions with chemotherapy
Bohm 1999	50	Prospective	"All eligible patients were assessed for response and toxicity. The toxicity was moderate with lack of significant nephrotoxicity. Neurotoxicity and ototoxicity were acceptable and in no patient was treatment discontinued for those toxic effects."	"overall survival…appeared to be better than expected with the current therapy in this group with advanced/bulky disease."
Schmidinger 2000	20	PCRT	Intensity of hematologic toxicity was significantly less pronounced in patients treated with glutathione than in the control group.	GSH arm: 55% remission (CR 9%; 46 partial) vs. placebo: 50% partial remission only. Antitumor efficacy of CDDP is not impaired by GSH
Di Re 1993	79	Prospective	The severity of peripheral neurotoxicity and ototoxicity were apparently less than has been reported with other high-dose cisplatin regimens	"The present study clearly documents the safety of a high-dose cisplatin regimen including GSH. The feasibility of this protocol is supported by a lack of significant nephrotoxicity and by the acceptable neurotoxicity. This unexpected finding may have important clinical implications, since neurotoxicity has emerged as the dose-limiting toxicity in high-dose regimens [4]."
Milla 2009	52	PCRT	"Statistically significant reduction of neurotoxicity in the GSH arm, together with statistically significant reduction of sural sensory nerve conduction in the placebo arm but not in the GSH arm."	Focused on PK – identified no interaction with oxaliplatin
15 clinical trials	932			

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Market Data

- FDA 503B product reporting – end 2021
  - 5 Outsourcing Facilities report making 7 presentations of glutathione

- To the best of our ability, we estimate ~30,000 prescriptions for glutathione are written per year in the USA for cystic fibrosis and chemotherapy induced neuropathy.

Market Data

- McGuff Compounding Pharmacy Post Market Data
  - One of 881 Sterile Compounding Pharmacies Licensed by California Board of Pharmacy

- Glutathione Data Capture: 8/2008 to 4/31/2022 (13 Years 8 Months)

- 372,067 Number of vials dispensed:
- 86,671 Number of prescriptions received
- 3,614 Number of unique doctors who prescribed Glutathione
- 0 Serious Adverse Events Reported (as defined by MedWatch)

FDA's Criteria for Evaluation

FDA published notice of a final rule establishing the criteria for evaluation of bulk drug substances for inclusion on the 503A Bulks List (84 FR 4696):

1. The physical and chemical characterization of the substance;
2. Any safety issues raised by the use of the substance in compounded drug products;
3. The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and
4. Historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature.

In evaluating the candidates for the 503A Bulks List under these criteria, the Agency will use a balancing test. Specifically, the Agency will consider each criterion in the context of the others and to balance them, on a substance-by-substance basis, to decide whether a particular substance is appropriate for inclusion on the list

Final Summary

- No evidence from peer reviewed literature of significant toxicity or patient harm from inhaled, injected, or oral compounded glutathione
- 7 published trials for CF, with 280 patients
- 15 published trials for use in chemotherapy, with 932 patients
- No FDA approved product for CIPN
- FDA approved CF products are not curative, do not replace the need for glutathione
- Glutathione (L) Reduced EP (Pharma Grade) available to compounders in USA
- Formulations of glutathione are expected to be stable with proper formulation technique and controls, including pH

(L): levorotatory
EP: European Pharmacopoeia

Safety and Efficacy of Copper Depletion with Tetrathiomolybdate as a Therapeutic Strategy

Pharmacy Compounding Advisory Committee Meeting

June 8, 2022

Mark Rosenberg, MD
President and Medical Director,
Advanced Medical Therapeutics
& Integrative Cancer Therapeutics

On Behalf of Pharmacy Solutions

Copper and Cancer

nature biotechnology
ARTICLES
https://doi.org/10.1038/s41587-020-0707-9

Check for updates

Mitochondrial copper depletion suppresses triple-negative breast cancer in mice

Liyang Cui[1], Arvin M. Gouw[2], Edward L. LaGory[3], Shenghao Guo[4], Nabeel Attarwala[4], Yao Tang[5], Ji Qi[6], Yun-Sheng Chen[1,7], Zhou Gao[8], Kerriann M. Casey[9], Arkadiy A. Bazhin[10], Min Chen[1], Leeann Hu[11], Jinghang Xie[1], Mingxi Fang[1], Cissy Zhang[4], Qihua Zhu[1,12], Zhiyuan Wang[4], Amato J. Giaccia[3], Sanjiv Sam Gambhir[1], Weiping Zhu[5], Dean W. Felsher[2], Mark D. Pegram[13], Elena A. Goun[10], Anne Le[4] and Jianghong Rao[1]✉

CANCER RESEARCH | TUMOR BIOLOGY AND IMMUNOLOGY

Intratumoral Copper Modulates PD-L1 Expression and Influences Tumor Immune Evasion

Florida Voli[1,2], Emanuele Valli[1,2], Luigi Lerra[1], Kathleen Kimpton[1,3], Federica Saletta[1,4], Federico M. Giorgi[5], Daniele Mercatelli[5], Jourdin R.C. Rouaen[1], Sylvie Shen[6], Jayne E. Murray[1], Aria Ahmed-Cox[1,2,3], Giuseppe Cirillo[7], Chelsea Mayoh[1,2], Paul A. Beavis[8,9], Michelle Haber[1], Joseph A. Trapani[8,9], Maria Kavallaris[1,2,3], and Orazio Vittorio[1,2,3]

ARTICLES
https://doi.org/10.1038/s41556-020-0481-4
nature cell biology

Check for updates

Copper is an essential regulator of the autophagic kinases ULK1/2 to drive lung adenocarcinoma

Tiffany Tsang[1,2,4], Jessica M. Posimo[1,4], Andrea A. Gudiel[1], Michelle Cicchini[1], David M. Feldser[1,3] and Donita C. Brady[1,3]✉

Although the transition metal copper (Cu) is an essential nutrient that is conventionally viewed as a static cofactor within

nature COMMUNICATIONS

ARTICLE
https://doi.org/10.1038/s41467-020-14698-y OPEN

Check for updates

Inflammation mobilizes copper metabolism to promote colon tumorigenesis via an IL-17-STEAP4-XIAP axis

Yun Liao[1,2,9], Junjie Zhao[1,9], Katarzyna Bulek[1,3], Fangqiang Tang[1], Xing Chen[1], Gang Cai[1], Shang Jia[4], Paul L. Fox[5], Emina Huang[6], Theresa T. Pizarro[7], Matthew F. Kalady[6], Mark W. Jackson[7], Shideng Bao[6], Ganes C. Sen[1], George R. Stark[6], Christopher J. Chang[4,8] & Xiaoxia Li[1]✉

Increasing interest from several research groups in modulating copper bioavailability as a therapeutic strategy

nature reviews cancer

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Perspective | Published: 11 November 2021

Connecting copper and cancer: from transition metal signalling to metalloplasia

Eva J. Ge, Ashley I. Bush, Angela Casini, Paul A. Cobine, Justin R. Cross, Gina M. DeNicola, Q. Ping Dou, Katherine J. Franz, Vishal M. Gohil, Sanjeev Gupta, Stephen G. Kaler, Svetlana Lutsenko, Vivek Mittal, Michael J. Petris, Roman Polishchuk, Martina Ralle, Michael L. Schilsky, Nicholas K. Tonks, Linda T. Vahdat, Linda Van Aelst, Dan Xi, Peng Yuan, Donita C. Brady ✉ & Christopher J. Chang ✉

nature COMMUNICATIONS

ARTICLE
https://doi.org/10.1038/s41467-021-27559-z OPEN

Check for updates

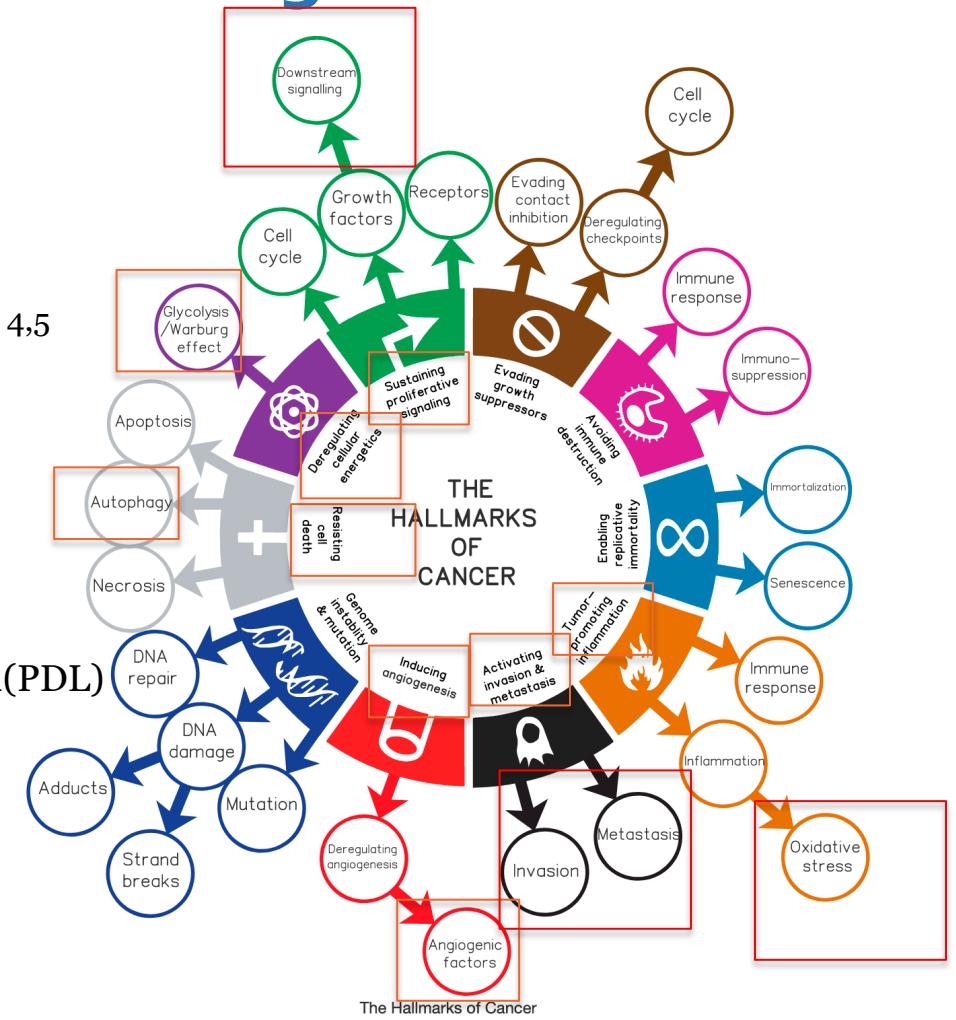
Copper depletion modulates mitochondrial oxidative phosphorylation to impair triple negative breast cancer metastasis

Divya Ramchandani[1], Mirela Berisa[2], Diamile A. Tavarez[1], Zhuoning Li[3], Matthew Miele[3], Yang Bai[1,4], Sharrell B. Lee[1], Yi Ban[1], Noah Dephoure[5], Ronald C. Hendrickson[3], Suzanne M. Cloonan[6,7], Dingcheng Gao[1,8,9], Justin R. Cross[2], Linda T. Vahdat[10]✉ & Vivek Mittal[1,8,9]✉

Copper as a Therapeutic Target

Involved in these processes:

- Angiogenesis [1,2,3]
- Mitochondrial Respiration[8,9]
- Stromal and Collagen Remodeling [4,5]
- Oxidative stress [10]
- Invasion [4,5,7]
- Migration [4,5,7]
- Regulates expression of
  Programmed Cell Death-Ligand 1(PDL) in neuroblastoma[8]



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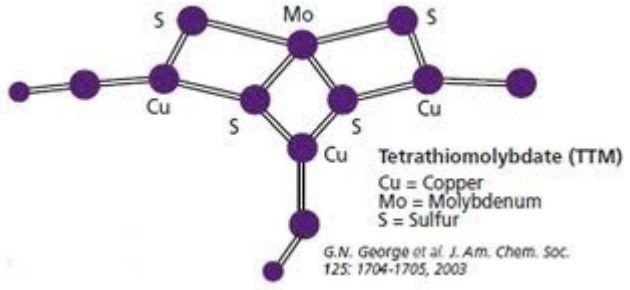
Copper Depletion with Tetrathiomolybdate(TM)

- Inactivates copper chaperones and decreases incorporation into copper-containing enzymes[1]
- Phase 3 trial in Wilson's disease underway (NCT03403205)
- Mouse models of cancer show tumor regression[2,3,4]
- Phase I/ II trials in overt disease with stable disease as best response [5,6,7]
- Phase 2 study in high risk for recurrent breast cancer [8,9,10]

Tetrathiomolybdate (TM)



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Safety Data TM in Advanced and High-Risk Cancer

Author	Disease	Setting	Number patients	Neutropenia (G3/4)	Febrile Neutropenia	Anemia (G3/4)	GI (N, V or D) G3/4)	Other (G3/4)	
Redman[1]	Stage 4 Renal	TM alone	15	11/15	None	None	None		
Henry[2]	Stage 4 Prostate	TM alone	19	3/19			1/28	Hematuria(1); lymphopenia (4); myalgias (1); unstable angina	
Pass[3]	Resected mesothelioma	TM alone	30	16/30	None	4/30	1/30		
Schneider[4]	Resected esophageal	TM alone	48	1/48	None		3/48		
Gartner[5]	Stage 4 Colorectal	With IFL chemo	28	9/28					

Gastro-intestinal (GI); nausea (N), vomiting(V), diarrhea(D); Grade ¾; IFL chemo = irinotecan/5FU/Leucovorin

Reversible neutropenia most prominent side effect noted in these trials

[1]Redman B Clin Cancer ResVol. 9, 1666–1672, May 2003; [2]Henry NL et al. Oncology 2006;71:168–175; [3]Pass H et al. Ann Thorac Surg 2008;86:383–90; [4]Schneider B et al. *Invest New Drugs*. 2013 April ; 31(2): 435–442 ; [5] Gartner E et al. Invest New Drugs. 2009 April ; 27(2): 159–165

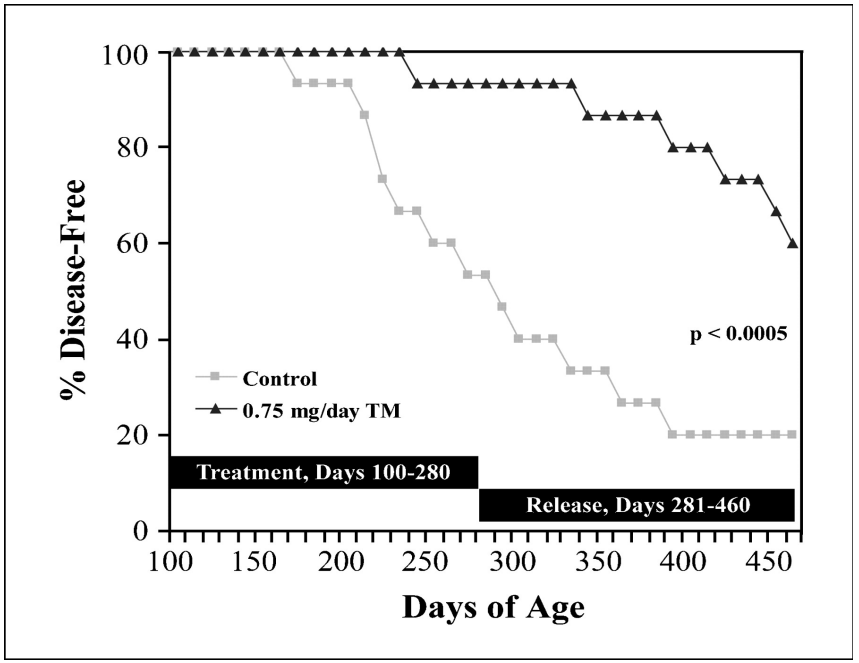
Please note that AE are reported in this toxicity table and incidence per patient instead of incidence per cycle.

TM Prevents Breast Cancer Metastases(Mets) in a Pre-Clinical Model

Experiment:

- MMTV-Her2neu randomized to TM x 180 days *vs* water control
- Control mice developed lung metastases at day 205 and TM treated mice did not
- When TM therapy withdrawn, the mice developed lung mets at a median of 2 weeks later
- <u>Conclusion:</u> TM therapy prevented the development of overt metastases in this model

TM prevents lung mets but effect only seen when on TM therapy.



Pan Q et al. Cancer Res. 2002 Sep 1;62(17):4854-9; Pan Q et al. Clin Cancer Res 2009;15:7441-7446

Concept

- Targeting the tumor microenvironment through a copper depletion strategy can prevent metastases
- Copper depletion with oral tetrathiomolybdate (TM) is safe and well tolerated

Strategy

- Conduct a Phase 2 study of TM in high risk for recurrent breast cancer
- Embed significant amounts of science with the study to understand the mechanism of action

Pilot Trial: Phase 2 Trial of Tetrathiomolybdate in High Risk for Recurrence Breast Cancer

Breast cancer at high risk of relapse and No Evidence Of Disease(NED)
N= 75

Daily oral TM For 2 years to achieve Ceruloplasmin(Cp) Target
≤ 17 mg/dL

High Risk

- Stage III and IV NED breast cancer
- Stage II Triple Negative Breast Cancer (TNBC)

No Evidence of disease (NED)

- Physical exam
- Labs: complete blood count (CBC), comprehensive metabolic panel(CMP), tumor markers
- Imaging: CT scan with bone scan or PET/CT Scan

Local and systemic therapy:

- Completion of standard therapy

accrual completed in 2014

Primary endpoint:

- **Vascular endothelial growth factor receptor 2** (VEGFR2)+ **endothelial progenitor cells(EPC)**

Secondary endpoints:

- Progression-Free Survival
- Overall Survival
- Vascular endothelial growth factor receptor 1 (VEGFR1)+ Hematopoietic cells (HPC)
- Adverse events
- Circulating markers in the tumor microenvironment

Chan et al. Clinical Cancer Res 2017 Feb 1;23(3):666-676.

Phase 2 Trial of Tetrathiomolybdate In High Risk for Recurrence Breast Cancer

Breast cancer at high risk of relapse and NED

Daily oral TM For 2 years to achieve Cp target ≤ 17 mg/dL

Once every 4 weeks (1 cycle)

- Physical exam
- CBC, CMP, tumor markers
- Ceruloplasmin (Cp) level
- Flow cytometry for Bone-Marrow Derived (BMD) progenitors and other research blood (banked)

Once every six months

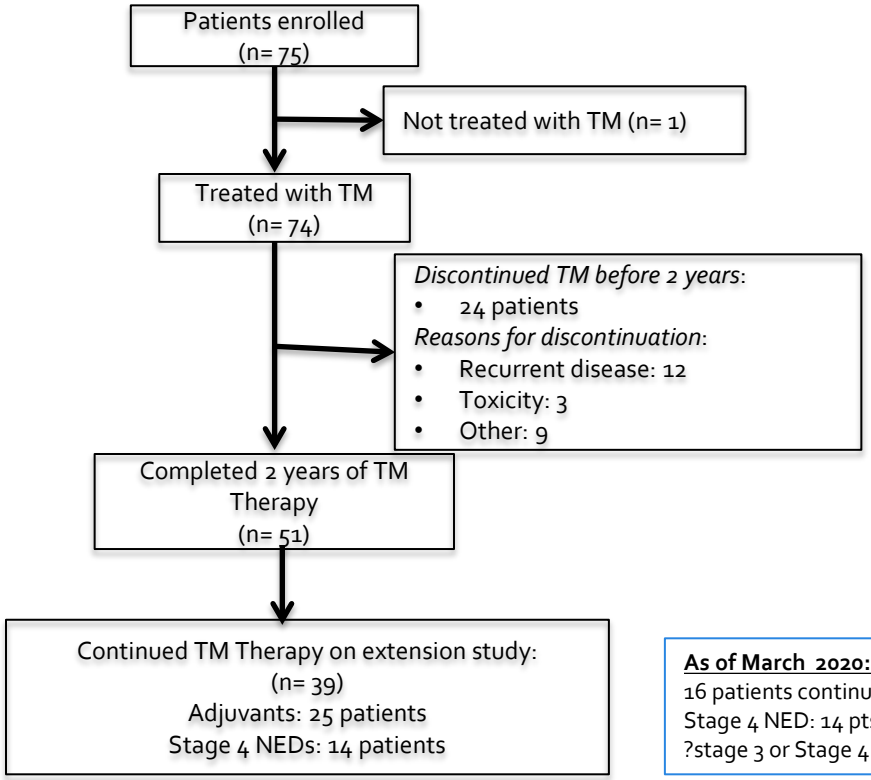
- CT with Bone Scan (BS) or PET/CT

Primary endpoint:
- VEGFR2+ EPCs

Secondary endpoints:
- Progression-Free Survival
- Overall Survival
- VEGFR1+ HPCs
- Adverse events
- Circulating markers in the tumor microenvironment

Chan et al. Clinical Cancer Res 2017 Feb 1;23(3):666-676.

Phase 2 Trial of Tetrathiomolybdate in High Risk for Recurrence Breast Cancer



Selected demographic variables	No. of patients (75)
Median Age, (range)	51 years (29-66)
AJCC Stage at Study entry, n (%)	
Stage 2	4 (5)
Stage 3	41 (55)
Stage 4 NED	30 (40)
Median tumor size in Stage 2/3 adjuvant pts, cm (range)	2.3 (1.2-7)
Median no. of positive lymph nodes in Stage 2/3 adjuvant pts, n (range)	6 (1-42)
Sites of Stage 4 disease, n • Chest wall/liver • Brain/bone only • Peritoneum/lung	 13/4 2/3 1/3
Luminal A or B/Her2neu/TNBC (%)	**40/12/48**

American Joint Committee on Cancer (AJCC)

As of March 2020:
16 patients continue on TM:
Stage 4 NED: 14 pts
?stage 3 or Stage 4 NED: 2 pts

Study closed due to loss of drug supply. Patients transitioned to non-Good Manufacturing Practices (GMP) TM

Chan et al. Clinical Cancer Res 2017 Feb 1;23(3):666-676.

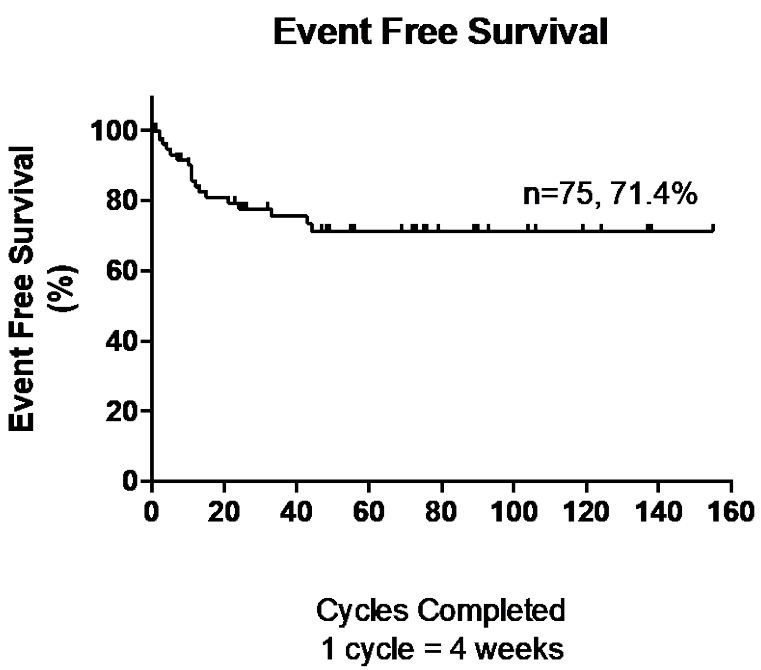
Phase 2 TM Trial Adverse Events

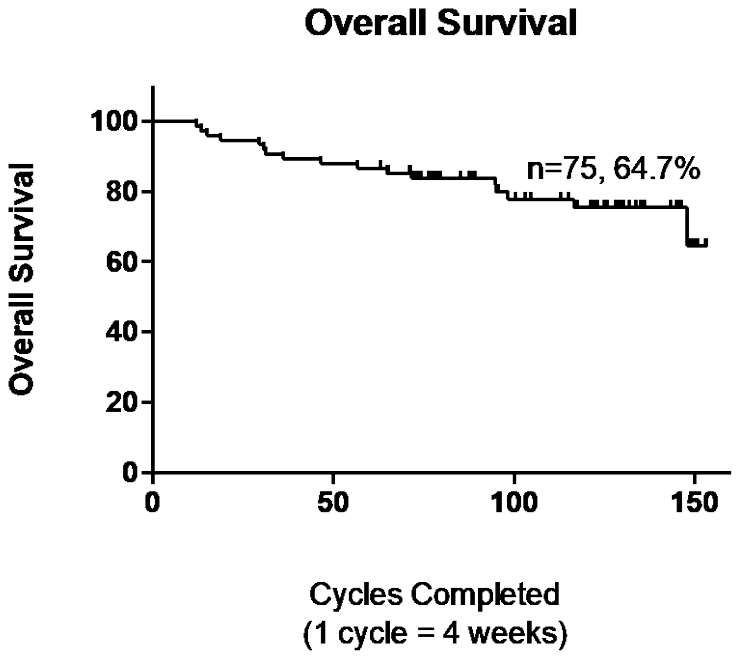
Number of cycles complicated by adverse events (total cycles = 3478)			
Adverse Event		**N (%)**	**N (%)**
		All Grades	Grade 3/4
Hematologic			
	Anemia	324 (9.0)	1 (0.03)
	Neutropenia	41 (12.1)	59 (1.7)
	Febrile Neutropenia	1 (0.03)	1 (0.03)
	Leukopenia	427 (12.3)	29 (0.8)
	Thrombocytopenia	31 (0.9)	0 (0)
Gastrointestinal			
	Sulfur Burps	929 (26.7)	0 (0)
	Nausea	76 (2.2)	0 (0)
	Vomiting	8 (0.2)	0 (0)
	Diarrhea	46 (1.4)	0 (0)
	Constipation	7 (0.2)	0 (0)
	Abdominal Pain	1 (0.03)	0 (0)
General			
	Fatigue	798 (22.9)	6 (0.2)
Neurologic			
	Dizziness	26 (0.7)	0 (0)
	Neuropathy	574 (16.5)	5 (0.1)

Grade 3 or 4 AEs < 3%

Data cutoff 1/1/2020

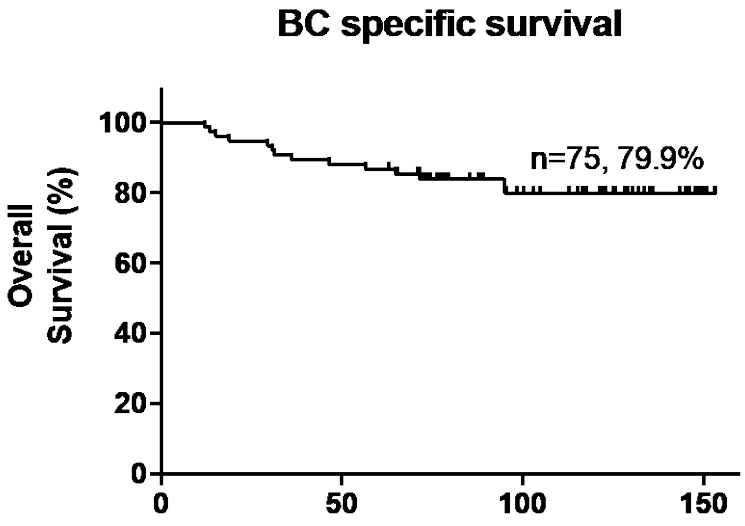
Phase 2 Trial of Tetrathiomolybdate in High Risk for Recurrence Breast Cancer: Outcome

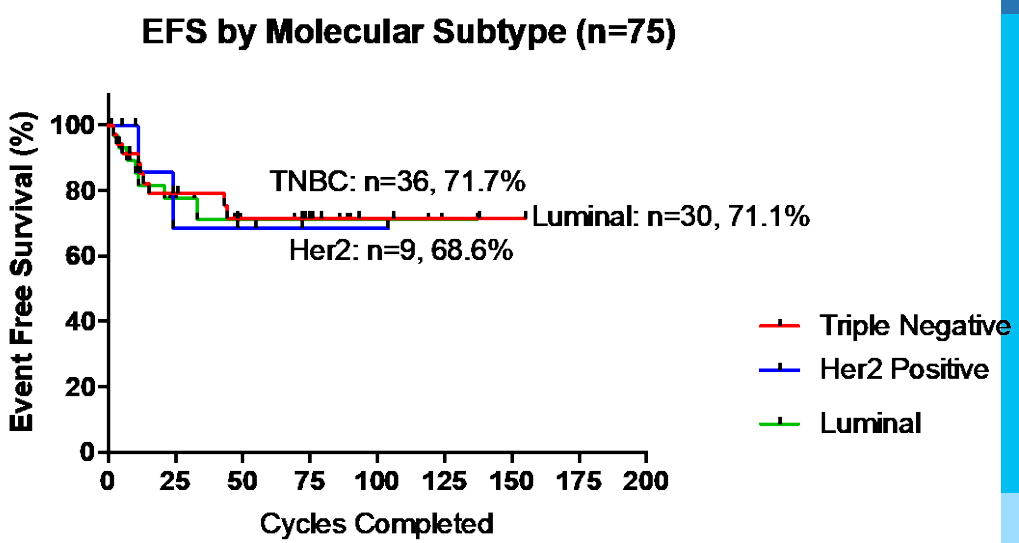




Median Follow Up(FU) 9.4 years
Event Free Survival (EFS)
Overall Survival (OS)

Phase 2 Trial of Tetrathiomolybdate in High Risk for Recurrence Breast Cancer(BC): Outcome



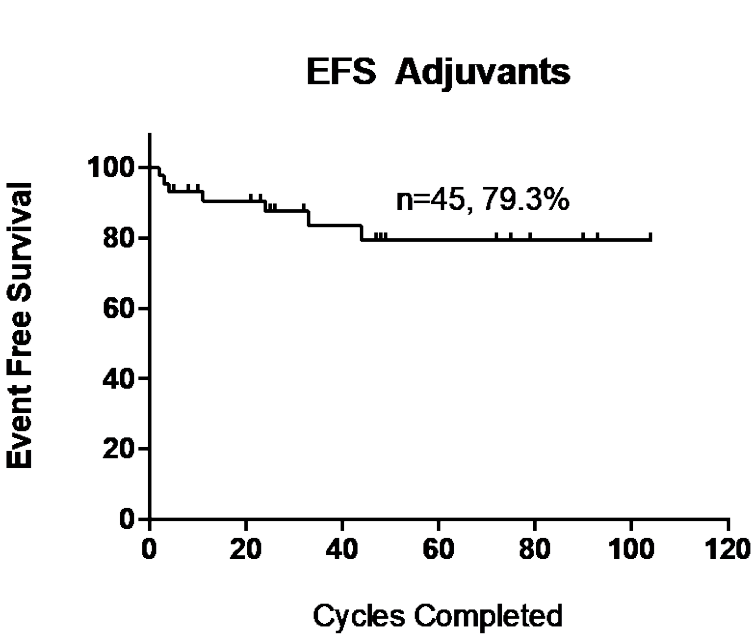


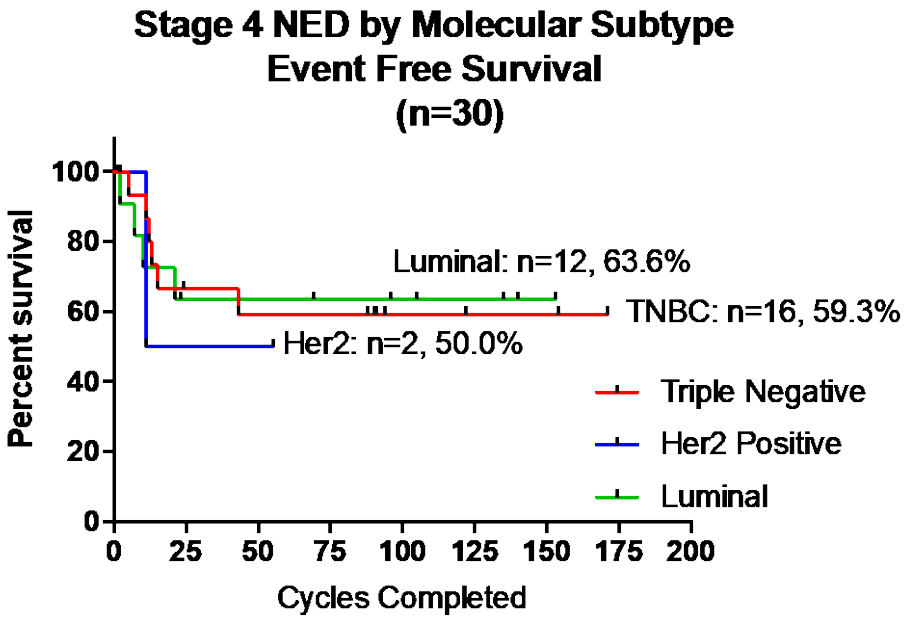
Her2=human epidermal growth factor receptor 2

Median Follow Up(FU) 9.4 years
1 Cycle= 4 Weeks
Event Free Survival (EFS)
Overall Survival (OS)

No difference in outcome based on molecular subtype

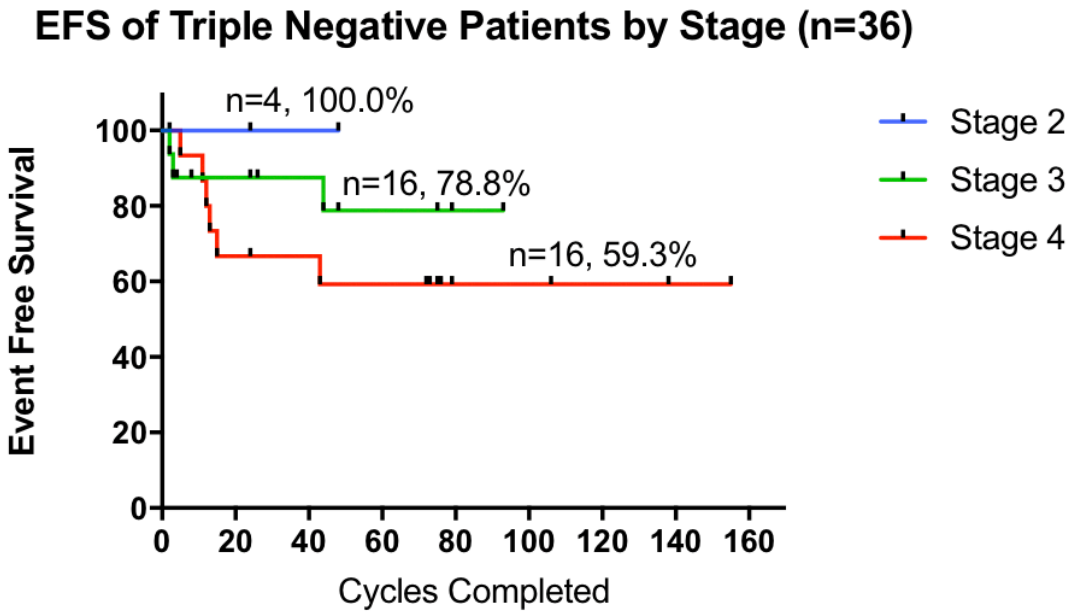
Phase 2 Trial of Tetrathiomolybdate in High Risk for Recurrence Breast Cancer: Outcome





Median Follow Up(FU) 9.4 years
1 Cycle= 4 Weeks
Event Free Survival (EFS)
Overall Survival (OS)

Phase 2 Trial of Tetrathiomolybdate In High Risk for Recurrence Breast Cancer: Outcome in TNBC



Median FU 9.4 years
1 cycle = 4 weeks

TNBC=Triple Negative Breast Cancer

Expected outcome in stage 4 TNBC: median OS 11 months.

Scientific Correlatives

- In copper depleted patients [1,2,3]
  - Reduction in VEGFR2+ EPCs
  - Reduction in **L**ysyl Oxidase Like 2 (LOXL-2)
  - Normalization of the collagen microenvironment
  - Improved EFS in adjuvant pts with Antioxidant 1 Copper Chaperone (ATOX 1) expressing primary tumors
- In preclinical models:
  - No effect in primary tumors but decrease in lung mets
    - Lung mets with marked reduction in LOX and collagen remodeling
  - Reprogramming of the metabolic microenvironment (increase in Adenosine Monophosphate-Activated Protein Kinase (AMP kinase) and shift towards glycolysis[4]
  - Reduction in Myeloid-Derived Suppressor Cells**(**MDSC) in primary tumors of TM treated mice[2]

[1]Chan et al. Clinical Cancer Res 2017;[2]Liu et al. NPJ Breast 7, 108. 2021; [3]Blockhuys et al. Biomedicines 2021;[4]Ramchandani et al, Nat Comm 2021

Next Steps

- Randomized phase 2 study in high risk for recurrence TNBC planning underway
  - Support by
    - National Cancer Institute Research Project Grant(NCI RO1)
    - NCI NExT Program
    - Gateway Foundation
    - Breast Cancer Research Foundation (BCRF)
    - Translational Breast Cancer Research Consortium (TBCRC)
    - Philanthropic Donors
- Investigation underway in high-risk Non-Small Cell Lung Cancer (NSCLC) (pre-clinical with clinical trial development) and $BRAF^{v600}$ melanoma
- Expanding correlative science in completed phase 2 study in Breast Cancer