INTERNATIONAL
IV NUTRITIONAL THERAPY
GLOBAL PHYSICIAN EDUCATION

Germanium and Botanicals

Advanced IV Therapy: Chronic Disease and Infections
by
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Germanium - "Ekasilicon"

- Metalloid
- Appears metalic
- Non metal properties
- Column Group IV A (Carbon, Silicon, Germanium, Tin, Lead)
- By product of zinc ore processing:coal
- Trace mineral
- Cystaline structure same as a diamond

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inorganic

- More abundant in the Earths crust than gold, silver, mercury and cadmium
- Classified as a semi-metal (essential) with carbon, lead, silicon, and tin
- Electrical properties between metal and insulator
- Toxicity
  - Low in mammals (But, NOT the form used in IV Therapy!)
  - High in certain strains of bacteria

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Inorganic

- Uses
  - Radios
  - Infrared scopes
  - Wide angle camera lenses
  - Microscope lenses
  - Silicon-germanium is becoming a very popular semiconductor faster than silicon alone
  - Solar cells

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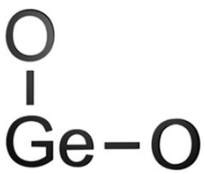
inorganic

- Germanium dioxide
  - germanium oxide
  - germania



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inorganic

- Safety and Toxicity
- The 'other' germanium
  - Inorganic germanium is harmful in large doses
  - Typically used for topical applications
  - Germanium dioxide or germanium citrate lactate is nephrotoxic/ and pulmonary tox.

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inorganic

- Renal dysfunction/failure
  - Vaculor degeneration of renal tubular epithelial cells
  - Ø proteinuria,hematuria or glomerular change
- Central and peripheral nerve toxicity
- Cardiomyopathy
- Liver damage
- Bone marrow

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Inorganic

- Symptoms
  - Anemia
  - Weight loss
  - Fatigue
  - Gastrointestinal dysfunction
  - Kidney dysfunction
  - Muscle weakness
    - skeletal

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Organic

- **CURRENTLY NOT AVAILABLE IN USA**

Kazuhiko Asai

- Developed research and clinical use (germanium by product of coal)
  - "I have been led to believe the existence of something in germanium that cannot be fully explained in terms of science in its present stage of development, when I see that obstinate diseases for which modern medicine is powerless are successfully cured by our germanium therapy." Kazuhiko Asai
- 1967, Mironov synthesizes water-soluble organic form

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organic

- Polymorphic - can manifest as differing crystalline, particle size and weight distributions in solid form. In aqueous solution they are stable and identical.
- Ubiquitous in seawater, plants, and animal blood and tissues as an essential trace element.
- Plants with the most abundant amounts
  - Shelf fungus/Trametes Cinnabarina 800-2000 ppm
  - Garlic 754ppm
  - Ginseng 250-300ppm
  - Sansukon/Codonopsis 257ppm
  - Suchi/Angelica pubescens 242ppm
  - Bandai Moss 215ppm
  - Waterna/Trapa japonica 239ppm
  - Comfrey 152ppm
  - Bodhorne Seed/Lycium 124ppm
  - Wisteria gall 108 ppm
  - Uthoapermum officinale 88ppm
  - Aloe 77ppm
  - Chlorella 76ppm
  - Bandai Udo/Aralia cordata 72ppm
  - Pearl Barley 50ppm

(Asai 1980)

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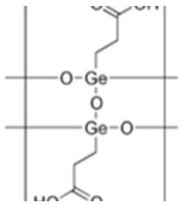
organic



- Germanium sesquioxide
  - Bis (2-carboxyethylgermanium) sesquioxide (CEGS)
  - 2-carboxyethylgermasesquioxane
  - Propagermanium

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organic

- LD 50 >6.3g/kg body wt in mice
  - 10g/kg in rats
  - 750mg/kg qd over 1 yr in rats (Asano etal, 1994)
- No acute or chronic toxicity has been associated with this form oral or IV.
- Organic Sesquioxide germanium appears safe at large doses.
  - Increases oxygen due to its affinity for Hydrogen (dehydrogenizing-detoxing)
  - Carrying oxygen to hypoxic tissues

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Organic Indications

- Cancer and Metastasis
  - Tumor necrosis
- Rheumatoid Arthritis
- Lung dz
  - Asthma, Pneumonia,
- Depressive Psychosis mental d/o
- 'Stress'
- Eye Diseases
- Viral Diseases
- Cardiac / HTN
- Adrenal
- Epilepsy
- Prostate
- Dermal
  - Eczema,shingles,warts
- Thyroid
- G.I.
- Pain
  - external applications (Asai, 1980)

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organic

- Affects enzyme activity
  - Activation
  - Inhibitory
- Elevation in SOD
- enhances NK activity
- induces IFN-g
  - inhibit tumor growth
- Increase development of T-cells
- Cytoplasmic enzyme is inhibited:
- LDH (lactate dehydrogenase)
- Inhibit viral HSV-1
- Influence on the DNA/RNA
- Enhancement of semiconductor properties regulating gene expression
- Apoptotic

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organic

Contraindications/ Precautions
- Renal failure
- With nephrotoxic drugs
- Diabetes

Caution:
- Children
- Pregnancy
- Nursing Mothers

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organic

- Side Effects with high dosing
  - Emesis (GI effects common even in IV use – Dose dependent)
  - Nausea
  - Diarrhea
  - Dermal lesions/Rashes
  - Neurological
  - Resolves with discontinued use
    - Caution to check labs if long term use

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organic

- Dosages (Oral)
  - Capsules 25 mg, 150 mg
  - Sublingual Tablets 25 mg, 150 mg
  - No toxic effects with 120mg/kg/day of germanium sesquioxide over a 24 wk period
  - Prevention: 150 mg daily
  - Serious Illness: up to 2000 mg daily

  - Human studies have shown no side effects with 25, 50, and 75 mg/kg dosages.

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organic

Intravenous
- 100mg/ml
  - Compounded per order
  - Typical 100mg/ml 1-5cc
- Excretion
  - 24-72 hours
  - Water soluble

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Curcumin IV

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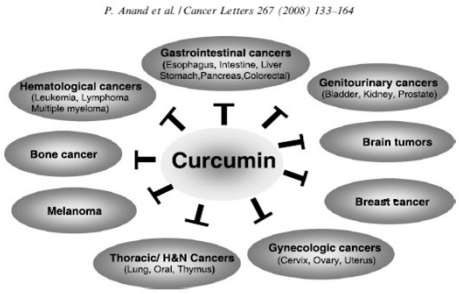

Fig. 3. Various cancers against which curcumin has potential for prevention and treatment.

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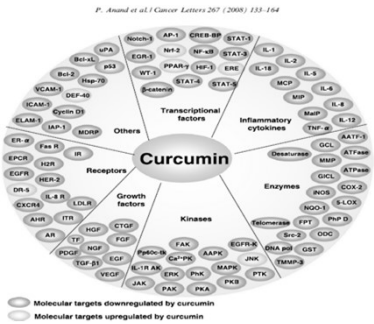

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IV Curcumin – Not all created equal:

A significant difficulty in describing the infusion of curcumin is the variety of potential forms of infusion product compounded. This paper describes mainly the solution form (3 below). We have additionally used form "2" below and find it more phlebogenic. No extrapolation of the clinical data presented herein should be made to forms other than a true solution of curcumin ("3" below).

[1] Lipid (in a phospholipid Liposphere). Very hard to make properly and may be quite effective. Dripped slow like phosphatidylcholine IV.

[2] Curcumin in Cyclodextrin. Acts like the lipospheric form. Faster administration is possible but still a phlebitis potential if run too quickly.

[3] True Solution of Curcumin: Stabilized with a non-bound agent for solubility. Infusion rate is slow but is very vein tolerant

[4] Water Soluble solution. Highly alkaline to the point if not dilute will cause significant phlebitis and pH changes.

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Curcumin IV Concerns:

- Reactions:
  - 2 anaphylactic or anaphylactoid observed to date.
  - Some transient 'manic' symptoms in a minority of patients.
  - Peripheral heat and hand foot itching has happened at doses above 20 mg/mL in a minority of patients. Duration of 1-2 days.
  - Transient (lasting seconds to minutes) central chest heat feeling.
  - Skin rash, redness, dizziness all reversed with a hydration IV of 500 mL NS
- Variable dosing for different purposes:
  - Anti-tumor effect as a monotherapy likely at 20 – 40 mg/Kg
  - Cytokine manipulation effect may occur at 100 – 500 mg total

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Dilution

- Many of the reactions appear to not occur with better dilution of the curcumin.
- Our experience has shown that curcumin should not be administered at a greater dilution than 100 mg in 100 mL of saline or D5W.
- Most patients tolerate 400-500 mg in a 500 mL IV bag / 800 – 1000 mg per 1 Liter bag.

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Administration Speed

- Speed is variable and based on patient tolerance.
- At 20 – 40 mg / Kg doses we find the following:
  - At the above dilutions the first IV should run at 5 to 7 mL / minute.
  - If tolerated then a rate of 7 – 10 mL / minute is often tolerated.
- At low dose (500 mg or less) we find:
  - Most doses 50 – 500 mg are given in 500 mL IV
  - AT this dose we run the IV at 7 - 10 mL / min.

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Dosing

- For cytokine manipulation, autoimmune cases and potentially pain cases we find the following doses useful:
  - 1.5 – 10 mg / Kg

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Clinical Notes:

Screening:
- Intolerance to oral curcumin excludes use in the IV setting
- Lab studies:
  - CBC, Chemistry panel (Metabolic panel including electrolytes, bilirubin, AST/ALT, eGFR/BUN/CRE)

Cautions:
- Curcumin is a GRAS (generally recognized as safe) food additive by the FDA. Multiple studies using
- High doses of oral curcumin in humans have shown incredible safety [2,3,4].
- Potential cautions (not contraindications) include:
- Patients who exhibit any Type-1 symptoms post – test IV dose
- Patients on **anticoagulants** [5]:
  - Employ caution in dosing and monitor for increased bleeding.
- Patients with known **gallbladder disease** [6,7] or Patients who develop post-IV diarrhea:
  - Question patients. Increased right upper quadrant or right shoulder pain, or significant post-IV diarrhea may indicate a decrease in dose or discontinuation of therapy.

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Observed Reactions:

- 2 anaphylactic or anaphylactoid observed to date based on version that is no longer available.
- Nausea and vomiting:
  - In a minority of patients receiving over 10 mg/kg doses a transient and self-limited syndrome of dizziness, nausea and often vomiting has been observed. In each case the patient observed a dizziness and nausea combination of symptoms followed by vomiting of what appeared to be bile within 2-4 hours of finishing the infusion.
  - In each case the patient reported feeling “much improved” after the vomiting.
  - The vomiting was limited to one session following the infusion.
  - No patients have elected to discontinue high dose curcumin IV due to this experience.

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Observed Reactions:

- In each case the nausea and vomiting was either a lone event or two events in a row and were not at the beginning of therapy (most were after three to five infusions). Most only happened once.
- Our approach has been to decrease the body weight dose and ramp back up again to the therapeutic dose if tolerated.
- The proposed mechanism based on patient observations and clinical correlation is an aggressive choloretic effect sometime after the initiation of the infusion series that leads to increased biliary activity, nausea and the other symptoms.
- We do now recommend that patients consume a fiber supplement for bile sequestration before, during and the evening of the infusion. Psyllium husk at 5-10 grams per dose or cholestyramine at 2-4 grams per dose (all usual dose and administration cautions observed).
- Although only one in 30-50 infusions at doses over 10 mg/kg have reported this occurrence it is advisable to notify patients of the possibility in higher dose infusions and take preventive precautions (hydration and oral bile sequestrants).

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Observed Reactions:

- Some transient 'manic' / euphoric symptoms during and after the IV for up to 2-4 hours in a minority of patients.
- Peripheral heat and hand foot itching has happened at doses above 20 mg/mL in a minority of patients. Duration of 1-2 days.
- Transient (lasting seconds to minutes) central chest heat feeling.
- Skin rash, redness, dizziness all reversed with a hydration IV of 500 mL NS
  - Protocol is to stop the curcumin infusion and start the NS IV via piggy-back line. Infuse until the reaction stops and then (in most cases) re start the curcumin at a slower rate.
  - These patients will require a higher dilution on their next curcumin infusion.

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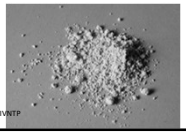
Quercetin



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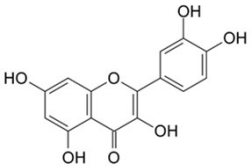
Quercetin

- Tyrosine Kinase Inhibition
- Immunomodulator
- Antioxidant
- Antiproliferative and Antimutagenic
- Apotototic
- Etc…



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Graefe EU, Derendorf H, Veit M. Pharmacokinetics and bioavailability of the flavonol quercetin in humans. Int J Clin Pharmacol Ther. 1999 May;37(5):219-33. PMID: 10363620

Flavonoids are plant polyphenolic compounds present in the daily diet. Latest epidemiological studies point to a crucial role of the flavonol quercetin in the prevention of cardiovascular diseases. It is assumed that this protective effect derives from the antioxidative capacity which quercetin shows in in vitro experiments. The antiproliferative and antimutagenic activities in vitro have made it a candidate for clinical trials in cancer therapy. Quercetin is also regarded as a putative active compound in various phytopharmaceuticals. However, in vivo data on the disposition, absorption, bioavailability, and metabolism of quercetin after intravenous and oral administration in humans are scarce and contradictory. The pharmacokinetic parameters following intravenous injection were determined in two studies. The elimination half-life was reported to be 2.4 h and 0.7 h, the volume of distribution at steady-state was 92.6 l and 6.2 l, and total body clearance was 34.6 lxh(-1) and 28.1 lxh(-1), respectively. Absorption after oral administration ranged from 0 to over 50% of the dose. These inconsistencies can partly be attributed to a lack of highly sensitive and specific assay methodology. The data available so far are insufficient to clarify whether or not quercetin can be held responsible for any protective or curative effect observed after oral intake.

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Guo Y, Mah E, Bruno RS. Quercetin bioavailability is associated with inadequate plasma vitamin C status and greater plasma endotoxin in adults. Nutrition. 2014 Nov-Dec;30(11-12):1279-86. doi:10.1016/j.nut.2014.03.032. Epub 2014 Jun 11. 10.1016/j.jad.2014.06.001. Epub 2014 Jun 11

OBJECTIVE:

Quercetin bioavailability exhibits high interindividual variation for reasons that remain unclear. We conducted a 24-h pharmacokinetic study to investigate whether individual differences in circulating antioxidants, oxidative stress and inflammation, and intestinal permeability affect quercetin bioavailability.

METHODS:

Healthy adults (n = 9 M/7 F; 34.3 ± 4.5 y; 27.0 ± 1.7 kg/m(2)) ingested 1095 mg quercetin aglycone with a standardized meal. Plasma antioxidants, biomarkers of oxidative stress and inflammation, and endotoxin were measured at baseline (0 h), and quercetin and its methylated metabolites isorhamnetin and tamarixetin were measured at timed intervals for 24 h.

CONCLUSIONS:

These findings suggest that vitamin C status and plasma endotoxin may be associated with interindividual variations in quercetin bioavailability. Greater quercetin absorption and bioavailability may be associated with poor vitamin C status and increased intestinal permeability in healthy adults.

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INTRAVENOUS QUERCETIN:

- Intravenous Quercetin has studied potential for increased bioavailability [1,2,4]
- Intravenous data in human subjects shows it to be tolerated and safe [1-3].

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Safety Dosage Phase 1 Trial

- 1700 mg/m2 dose-limiting nephrotoxicity was encountered
- **1400 mg/m2 (140 mg/kg)** weekly treatments with 2/10 having renal toxicity
- No cumulative renal impairment but fall of 19 (+/-) 8% GFR 24 hours after administration

- Clinical Cancer Research. 1996;2:659-68. Ferry DR, Smith, A., Malkhandi, J., Fyfe, D.W., deTakats, P.G., Anderson, D., Baker, J., Kerr, D.J. Phase 1 clinical trial of the flavonoid Quercetin: Pharmacokinetics and evidence for in vivo tyrosine kinase inhibition.

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Clinical Notes:

Dose: [1-4]
- Test dose at 1 mg/kg IV on the first day
- Subsequent doses could increase to (1400mg/m2) (BSA) OR 140 mg/kg if tolerated two - three times weekly
- Typical dosage for infections/MCAS: 300-500 mg

Administration:
- Intravenous dosing via either a central or peripheral line.
  - **Use a filtered line or add on filter set**
- Carrier solutions:
  - Per compounding pharmacy instructions
- Rate of administration: 60 to 240 minutes as tolerated by the patient
  - Monitor for signs of nausea which can be the first sign of a non-tolerated dose [3]
  - For allergic / anaphylactic reaction treat per standard protocol.
- Other IV compatibility:
  - Generally incompatible with other IV solutions in the same IV container

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Screening:

- Intolerance to oral Quercetin is a caution and may exclude use in the IV setting

- Lab studies:
  - CBC, Chemistry panel (Metabolic panel including electrolytes, bilirubin, AST/ALT/GGT, eGFR/BUN/CRE).

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Adverse Side Effects

- Headache
- Nausea
- Rash
- Tingling in arms and legs
- Hypersensitivity
- Renal toxicity

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References:

1. Gugler R., Leschik M., Dengler H. J.Disposition of quercetin in man after single oral and intravenous doses. European Journal of Clinical Pharmacology 1975, Volume 9, Issue 2-3, pp 229-234
2. Graefe EU, Derendorf H, Veit M. Pharmacokinetics and bioavailability of the flavonol quercetin in humans. Int J Clin Pharmacol Ther. 1999 May;37(5):219-33. PMID: 10363620
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6. Guo Y, Mah E, Bruno RS. Quercetin bioavailability is associated with inadequate plasma vitamin C status and greater plasma endotoxin in adults. Nutrition. 2014 Nov-Dec;30(11-12):1279-86. doi:10.1016/j.nut.2014.03.032. Epub 2014 Jun 11. 10.1016/j.jad.2014.06.001. Epub 2014 Jun 11

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Glycyrrhizic Acid

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Yasui S, Fujiwara K, Tawada A, Fukuda Y, Nakano M, Yokosuka O. Efficacy of intravenous glycyrrhizin in the early stage of acute onset autoimmune hepatitis. Dig Dis Sci. 2011 Dec;56(12):3638-47. doi: 10.1007/s10620-011-1789-5. Epub 2011 Jun 17. PMID: 21681505

Acute onset autoimmune hepatitis (AIH) shows acute presentation like acute hepatitis and does not have typical clinicopathological features of AIH. There is no gold standard for making the diagnosis. Therefore, losing the timing of starting immunosuppressive therapy, some of the cases develop into severe or fulminant form and have poor prognosis.

Our aim was to elucidate the efficacy of intravenous glycyrrhizin in decreasing alanine aminotransferase (ALT) level in the early stage of acute onset AIH.

Thirty-one patients were defined as acute onset AIH based on our uniform criteria, and were enrolled in this study. We prospectively treated 17 patients with sufficient doses (100 ml/day) of intravenous glycyrrhizin (SNMC) at an early stage (SNMC group), and treated 14 patients of severe disease with intravenous glycyrrhizin and corticosteroids (CS) (SNMC + CS group). We examined their clinical and biochemical features and treatment responses.

The ALT level could be controlled at an early stage using SNMC with no significant difference compared with SNMC + CS, and responsiveness to the therapy was determined by the disease severity at the time of starting therapy rather than the time duration from onset to therapy. Recovery rate was higher in the SNMC group than in the SNMC + CS group (P = 0.035).

The early introduction of sufficient doses of SNMC might prevent disease progression in patients with acute onset AIH. SNMC can be used safely and be useful for patients with difficult-to-diagnose acute liver disease as an 'initial' treatment tool to improve liver inflammation before starting disease-specific treatments.

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van Rossum TG, Vulto AG, Hop WC, Brouwer JT, Niesters HG, Schalm SW. Intravenous glycyrrhizin for the treatment of chronic hepatitis C: a double-blind, randomized, placebo-controlled phase I/II trial. J Gastroenterol Hepatol. 1999 Nov;14(11):1093-9. PMID: 10574137

BACKGROUND: In Japan, glycyrrhizin therapy is widely used for chronic hepatitis C and reportedly reduces the progression of liver disease to hepatocellular carcinoma. The aims of this study were to evaluate the effect of glycyrrhizin on serum alanine aminotransferase (ALT), hepatitis C virus (HCV)-RNA and its safety in European patients.

METHODS: Fifty-seven patients with chronic hepatitis C, non-responders or unlikely to respond (genotype 1/cirrhosis) to interferon therapy, were randomized to one of the four dose groups: 240, 160 or 80 mg glycyrrhizin or placebo (0 mg glycyrrhizin). Medication was administered intravenously thrice weekly for 4 weeks; follow up also lasted for 4 weeks.

RESULTS: Within 2 days of start of therapy, serum ALT had dropped 15% below baseline in the three dosage groups (P < 0.02). The mean ALT decrease at the end of active treatment was 26%, significantly higher than the placebo group (6%). A clear dose-response effect was not observed (29, 26, 23% ALT decrease for 240, 160 and 80 mg, respectively). Normalization of ALT at the end of treatment occurred in 10% (four of 41). The effect on ALT disappeared after cessation of therapy. During treatment, viral clearance was not observed: the mean decrease in plasma HCV-RNA after active treatment was 4.1 x 10(6) genome equivalents/mL (95% confidence interval, 0-8.2 x 10(6); P > 0.1). No major side-effects were noted. None of the patients withdrew from the study because of intolerance.

CONCLUSIONS: **Glycyrrhizin up to 240 mg, thrice weekly, lowers serum ALT during treatment, but has no effect on HCV-RNA levels. The drug appears to be safe and is well tolerated. In view of the reported long-term effect of glycyrrhizin, further controlled investigation of the Japanese mode of administration (six times weekly) for induction appears of interest.**

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van Rossum TG, Vulto AG, Hop WC, Schalm SW. Pharmacokinetics of intravenous glycyrrhizin after single and multiple doses in patients with chronic hepatitis C infection. A Clin Ther. 1999 Dec;21(12):2080-90. PMID: 10645755

Intravenous glycyrrhizin has been used in Japan for the treatment of chronic hepatitis for >20 years, although only a few reports of its pharmacokinetic profile after multiple intravenous doses in small numbers of Japanese patients have been published. The present study compared these Japanese data against the pharmacokinetic characteristics of glycyrrhizin after single and multiple intravenous doses in 35 European patients with chronic hepatitis C infection.

We administered 80, 160, or 240 mg glycyrrhizin 3 times/wk or 200 mg glycyrrhizin 6 times/wk for 4 weeks. Twenty-four-hour pharmacokinetic assessments were performed on day 1 and on or around day 14. Glycyrrhizin levels were determined by high-performance liquid chromatography. The mean (+/- SD) volume of distribution at steady state on day 1 in the 80-, 160-, 200-, and 240-mg groups were 67 +/- 11, 62 +/- 13, 54 +/- 7, and 66 +/- 8 mL/kg, respectively. The respective terminal elimination half-lives on day 1 were 7.7 +/- 2.8, 10.1 +/- 1.4, 9.0 +/- 2.3, and 8.6 +/- 2.1 hours. The area under the curve (AUC) increased linearly with doses < or =200 mg (r = 0.67; P < 0.001). No significant differences between day 1 and day 14 were found in any dose group, with the exception of AUC in the 200-mg group, which was significantly higher on day 14 compared with day 1 (P = 0.03). Comparing the European and Japanese data, the mean (+/- SD) AUC was 289 +/- 244 microg/h per mL for the former and 402 +/- 372 microg/h per mL for the latter; the half-life was 8.2 +/- 2.6 versus 8.8 +/- 9.0 hours; and the total clearance was 7.6 +/- 3.6 versus 8.5 +/- 5.7 mL/h per kg.

Thus our pharmacokinetic data are comparable to those from Japan. Glycyrrhizin's pharmacokinetics are linear up to 200 mg. Drug accumulation is seen after 2 weeks of treatment with 200 mg administered 6 times/wk.

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van Rossum TG, de Jong FH, Hop WC, Boomsma F, Schalm SW. 'Pseudo-aldosteronism' induced by intravenous glycyrrhizin treatment of chronic hepatitis C patients. J Gastroenterol Hepatol. 2001 Jul;16(7):789-95. PMID: 11446888

BACKGROUND AND AIMS:

Treatment with intravenous glycyrrhizin reduces the progression of liver disease caused by chronic hepatitis C (HCV) infection. Glycyrrhetinic acid, a metabolite of glycyrrhizin, inhibits the renal conversion of cortisol to cortisone by inhibiting the enzyme 11 beta-hydroxysteroiddehydrogenase in the kidney. The resulting excess of cortisol subsequently stimulates the mineralocorticoid receptor, leading to pseudo-aldosteronism with hypertension, hypokalemia and eventually renin and aldosterone suppression. The aim of this study was to evaluate the occurrence of pseudo-aldosteronism after treatment of chronic hepatitis C (HCV) patients with increasing doses of intravenous glycyrrhizin.

METHODS:

Forty-four HCV patients with chronic hepatitis or compensated cirrhosis were treated with intravenous glycyrrhizin 6 x 200 mg/week, 3 x 240 mg/week or 3 x 0 mg/week (placebo) for 4 weeks. In all patients, bodyweight, blood pressure and plasma concentrations of sodium, potassium, cortisol, DHEA-S (dehydroepiandrosterone sulfate), renin and aldosterone were measured before, and at 0 and 4 weeks after treatment.

RESULTS:

Within the placebo group, no significant changes were observed. Within the 1200 mg group systolic blood pressure was significantly higher at the end of treatment, while aldosterone was significantly lower; at the end of the follow-up period these values had returned to baseline. The changes from baseline in systolic and diastolic blood pressure at the end of treatment were significantly higher in the 1200 mg group compared to the placebo group. The changes in aldosterone and potassium concentrations at the end of treatment increased with increasing dosage, although not significantly.

CONCLUSION:

Hepatitis C virus patients with chronic hepatitis or compensated cirrhosis show minor reversible symptoms of pseudo-aldosteronism after treatment with 1200 mg glycyrrhizin weekly for 4 weeks.

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Glycyrrhizic Acid

- Safe in IV doses of 40 – 240 mg per day
  - Mixes well (generally) with water soluble IV formulas
- Common uses:
  - Viral infections
  - Inflammatory conditions / Atopy
  - General Immune Formulas
- Always watch pre and post vital signs

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Artesunate

- Artesunate (ART), a derivative of artemisinin
- ART is considered to produce a ROS burst
- Additionally, ART appears to be a synergist with oxidative therapies such as high dose ascorbic acid.
- Potential COX-2 inhibitor
  - **Artesunate inhibits the growth and induces apoptosis of human gastric cancer cells by downregulating COX-2. (Onco Targets Ther 2015 Apr 16;8:845-54)**

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ART Pharmacokinetics

Abstract

- The pharmacokinetics of good manufacturing process injection of artesunate (AS) were evaluated after single doses at 0.5, 1, 2, 4, and 8 mg/kg with a 2-minute infusion in 40 healthy subjects. Drug concentrations were analyzed by validated liquid chromatography and mass spectrometry system (LC-MS/MS) procedures. The drug was immediately converted to dihydroartemisinin (DHA), with elimination half-lives ranging 0.12-0.24 and 1.15-2.37 hours for AS and DHA, respectively. Pharmacokinetic model-dependent analysis is suitable for AS, whereas DHA fits both model-dependent and -independent methods. Although DHA concentration was superior to that of AS with a 1.12-1.87 ratio of area under the curve (AUC)(DHA/AS), peak concentration of AS was much higher than that of DHA, with a 2.80- to 4.51-fold ratio of peak concentration (C(max AS/DHA)). Therefore, AS effectiveness has been attributed not only to its rapid hydrolysis to DHA, but also to itself high initial C(max).
- Li Q, Cantilena LR, Leary KJ, Saviolakis GA, Miller RS, Melendez V, Weina PJ. Pharmacokinetic profiles of artesunate after single intravenous doses at 0.5, 1, 2, 4, and 8 mg/kg in healthy volunteers: a phase I study.Am J Trop Med Hyg. 2009 Oct;81(4):615-21. PMID: 19815876

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ART and CMV Virus

From the Abstract:

"This is the first report of treatment of cytomegalovirus infection with artesunate, for a stem cell transplant recipient with a newly identifie foscarnet-resistant and ganciclovirresistant DNA polymerase L776M mutation. Artesunate treatment resulted in a 1.7–2.1-log reduction in viral load by treatment day 7, with a viral half-life of 0.9–1.9 days, indicating a highly effective block in viral replication."

Shapira MY, et. Al. Artesunate as a Potent Antiviral Agent in a Patient with Late Drug-Resistant Cytomegalovirus Infection after Hematopoietic Stem Cell Transplantation. Clinical Infectious Diseases 2008; 46:1455–7

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ART and CMV Virus

And a cell line study bore out the superiority of Artesunate over other Artemesia compounds in CMV:

Flobinus A. Stability and antiviral activity against human cytomegalovirus of artemisinin derivatives. J. Antimicrob. Chemother. (2014) 69 (1): 34-40. doi: 10.1093/jac/dkt346

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ART and Bacteria

"Artemisinin and nine of its semisynthetic derivatives were tested for antibacterial activity against anaerobic, facultative anaerobic, microaerophilic and aerobic bacteria. Only anaerobic bacteria and gonococci showed sensitivity to artemisinin derivatives."

Shoeb HA, Tawfik AF, Shibl AM, el-Feraly FS. Antimicrobial activity of artemisinin and its derivatives against anaerobic bacteria. Journal of Chemotherapy (Florence, Italy) [1990, 2(6):362-367] (PMID:2128751)

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IND Protocol

CDC-005
IV Artesunate in the United States — December 19, 2016

IND Protocol: Intravenous Artesunate for
Treatment of Severe Malaria in the United States

IND Sponsor: Centers for Disease Control and Prevention (CDC)

CDC IRB #: 5012
IND #: 76,725

Revised December 19, 2016

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Human Use

Phase I-II data for IV administration of artesunate from a WHO summary by Dr. Melba Gomes indicate the following:

- Phase I trial: 2-4 mg/kg IV artesunate resulted in a reversible decrease in reticulocyte counts [section 14 i of WHO summary].
- Phase II trial: Approximately 15 mg/kg IV artesunate was administered over 3 days. Reversible increases in liver function tests were seen. Bradycardia was seen in the artesunate group and also in the simultaneous quinine group. [section 14 ii of WHO summary].
- Phase II trial: Approximately 6 mg/kg IV artesunate to patients with cerebral malaria resulted in SGPT elevations and BUN elevations that persisted until Day 6, the last day of observation. [section 14 vi of WHO summary].
- Intrarectal (IR), intramuscular (IM), and IV administration for severe malaria: IR administration resulted in "no major adverse effects" in 30 patients, other than dizziness, nausea, vomiting, and abdominal pain, which are components of acute malaria infection; 5 patients had tenesmus or extruded their suppositories, and had to have them reinserted; tenesmus was also recorded in African patients. IM administration resulted in a

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ART and AI

Wang Z, Qiu J et.al. Anti-Inflammatory Properties and Regulatory Mechanism of a Novel Derivative of Artemisinin in Experimental Autoimmune Encephalomyelitis. The Journal of Immunology, 2007, 179: 5958–5965.

Ethyl 2-[4-(12--artemisininoxy)]phenoxylpropionate (SM933) is a novel derivative of artemisinin, an herbal compound approved for the treatment of malaria. In this study, we show that SM933 has unique anti-inflammatory properties through regulation of signaling pathways, leading to amelioration of experimental autoimmune encephalomyelitis. The anti-inflammatory properties of SM933 were characterized by inhibition of encephalitogenic T cell responses that were altered to exhibit a Th2 immune deviation and reduced activity and concentration of NO and inducible NO synthase. The observed effect of SM933 was mediated through regulatory mechanisms involving the NFB and the Rig-G/JAB1 signaling pathways. …. **The study indicates that SM933 is a novel anti-inflammatory agent acting through defined signaling mechanisms and provides regulatory mechanisms required for effective drug targeting in treatment of autoimmune disease and inflammation.**

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ART and RA

Hou L, Block KE, Huang H. Artesunate Abolishes Germinal Center B Cells and Inhibits Autoimmune Arthritis. PLoS ONE 9(8): e104762. doi:10.1371/journal.pone.0104762

The antimalarial drug artemisinin and its derivatives exhibit potent immunosuppressive activity in several autoimmune disease models, however the mechanisms are not well-understood. This study was designed to investigate the therapeutic effects and the underlying mechanisms of the artemisinin analog artesunate using the K/BxN mouse model of rheumatoid arthritis. The well-studied disease mechanisms of K/BxN model allowed us to pinpoint the effect of artesunate on disease. Artesunate treatment prevented arthritis development in young K/BxN mice by inhibiting germinal center (GC) formation and production of autoantibodies. In adult K/BxN mice with established arthritis, artesunate diminished GC B cells in a few days. However, artesunate did not affect the follicular helper T cells (Tfh). In contrast to the spontaneous K/BxN model, artesunate treatment exerted minor influence on K/BxN serum transfer induced arthritis suggesting that artesunate has minimal effect on inflammatory responses downstream of antibody production.

Finally, we showed that artesunate preferentially inhibits proliferating GC B cells. These results identify GC B cells as a target of artesunate and provide a new rationale for using artemisinin analogues to treat autoimmune diseases mediated by autoantibodies.

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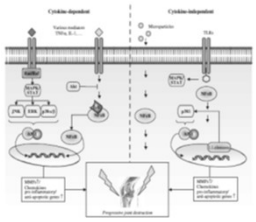
Rheumatology 2006;45:669–675

FIG. 2. Functional cross-talk of cytokine-dependent and cytokine-independent pathways of joint destruction in RA. Pivotal downstream signaling cascades including the MAP kinase system and the transcription factor NFkB are activated in the synovial fibroblast through pro-inflammatory cytokines such as TNFa, and various interleukins. Similar activation of these pathways, however, is also achieved by cytokine independent mechanisms, i.e. endogenous genetic elements (L1 retrotransposons), members of the innate immune system, namely various Toll-like receptors (reviewed in [17]) and novel mediators of cellular cross-talk such as immune cell-derived microparticles [27].



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ART and AI Biology

Shi C, Li H, Yang Y and Hou L. Anti-Inflammatory and Immunoregulatory Functions of Artemisinin and Its Derivatives. Mediators of Inflammation Volume 2015, Article ID 435713, 7 pages http://dx.doi.org/10.1155/2015/435713

Artemisinin and its derivatives are widely used in the world as the first-line antimalarial drug. **Recently, growing evidences reveal that artemisinin and its derivatives also possess potent anti-inflammatory and immunoregulatory properties.** Meanwhile, researchers around the world are still exploring the unknown bioactivities of artemisinin derivatives. In this review, we provide a comprehensive discussion on recent advances of artemisinin derivatives affecting inflammation and autoimmunity, the underlying molecular mechanisms, and also drug development of artemisinins beyond antimalarial functions.

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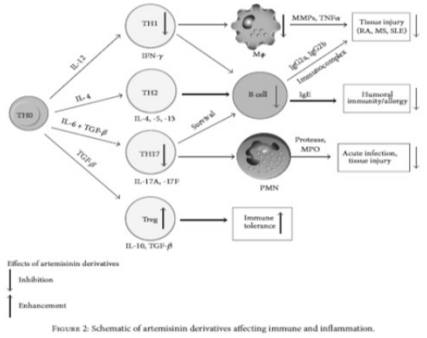

FIGURE 2: Schematic of artemisinin derivatives affecting immune and inflammation.

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ART and Lupus

Ouyang Jin1, 3, Huayong Zhang1, 3, Zhifeng Gu1, Shengnan Zhao1, Ting Xu1, Kangxing Zhou1, Bo Jiang1, Jie Wang1, Xiaofeng Zeng2 and Lingyun Sun1, 4 A Pilot Study of the Therapeutic Efficacy and Mechanism of Artesunate in the MRL/lpr Murine Model of Systemic Lupus Erythematosus. Cellular & Molecular Immunology. 2009;6(6):461-467.

Recent evidence indicates that artesunate has immunomodulatory properties that might be useful for treating autoimmune disease. In this study, we conducted a pilot study and explored the effect and mechanism of artesunate on the treatment of systemic lupus erythematosus using an MRL/lpr murine model. MRL/lpr mice were divided into control, cyclophosphamide (CTX) and artesunate treatment groups. Blood was collected to measure serum levels of creatinine, antinuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA) antibody. Twenty-four-hour urine was collected to measure levels of proteinuria. The concentration of monocyte chemotactic protein-1 (MCP-1) in serum and urine was measured. The expression of MCP-1 in kidney was detected by Western blot and immunohistochemistry assay, respectively. The expression of B cell activating factor (BAFF) in spleen was determined by real time-PCR and immunoblotting. We found that artesunate significantly increased the survival rate, body weight and blood leukocyte counts, and reduced the serum levels of ANA and anti-dsDNA antibody titer, 24 h urinary protein, and serum creatinine.

Our results indicated that artesunate could decrease MCP-1, major pro-inflammation cytokine, in serum, urine and kidney. We also found that the level of BAFF, the major B cell activation factor, was decreased in artesunate treated MRL/lpr mice. Its efficacy was comparable with that of CTX in this study. Taken together, we have demonstrated that artesunate can inhibit the progression of disease and reverse the pathologic lesion of lupus nephritis.

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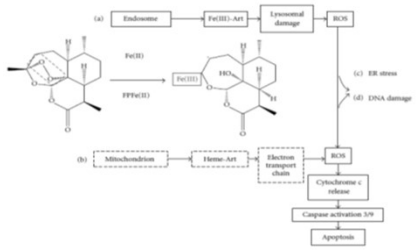
Maria P. Crespo-Ortiz and Ming Q.Wei. Antitumor Activity of Artemisinin and Its Derivatives: From aWell-Known Antimalarial Agent to a Potential Anticancer Drug .Journal of Biomedicine and Biotechnology. Volume 2012, Article ID 247597, 18 pages. doi:10.1155/2012/247597



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Oral Artemesinin

- Artesunate
- 200 mg per day oral Artesunate

- Artemesinin
- 300 mg three times per day x 3-5 days on 9-11 days off. (Pulsed dosage due to GI absorption issues). Best to take with food, preferably fat.

- Liposomal Artemesinin (more effective than oil)
- 1 cap three times per day for 3 days on 4 days off
- Or
- 3 tsp daily 3 days on 4 days off.

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Liposomal Artemisinin

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Protocol for IV Artesunate

- **D5W or NS**
  - **10-20 mL push or a 100 mL bag**
- **Infuse directly prior to HDIVC (High Dose IVC) for oxidative effect**
- **Infuse prior to other (non-oxidant) IV's in AI without chronic infection**
- **Doses are 60-120 mg**

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Toxicity

- Oral Toxicity

No toxicity in dogs using oral 45 mg/kg q6 hours x 3 weeks. Most common side effect was anorexia. Bioavailability wasn't high enough.

- Minimal AST, ALT elevations
- No neutropenia
- No anemia
- 556 mg/kg Artemether per day no toxicity in beagles
- No toxicity in monkeys which received 292 mg/kg (642 mg/pound) of Artemether over 1-3 months

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Artesunate References

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Paik IH, Xie S, Shapiro TA, Labonte T, Narducci Sarjeant AA, Baege AC, Posner GH. Second generation, orally active, antimalarial, artemisinin-derived trioxane dimers with high stability, efficacy, and anticancer activity. J Med Chem. 2006; 49:2731–4. [PubMed: 16640333]

Nam W, Tak J, Ryu JK, Jung M, Yook JI, Kim HJ, Cha IH. Effects of artemisinin and its derivatives on growth inhibition and apoptosis of oral cancer cells. Head Neck. 2007; 29:335–40. [PubMed:17163469]

Chen HH. et. al. Antimalarial dihydroartemisinin also inhibits angiogenesis. Cancer Chemother Pharmacol (2004) 53: 423–432. DOI 10.1007/s00280-003-0751-4

Chen HH. et. al. Inhibitory Effects of Artesunate on Angiogenesis and on Expressions of Vascular Endothelial Growth Factor and VEGF Receptor KDR/flk-1 Pharmacology 2004;71:1–9 DOI: 10.1159/000076256

Efferth T, et. al. The anti-malarial artesunate is also effective against cancer. International journal of Oncology. 2001. 18; 767-773

Yang J, et. al. Dihydroartemisinin is an inhibitor of ovarian cancer cell growth. Acta Pharmacol Sin 2007 Jul; 28 (7): 1045–1056. doi: 10.1111/j.1745-7254.2007.00612.x

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