QUINACRINE HYDROCHLORIDE

Pharmacy Compounding Advisory Committee
March 8-9, 2016

A.J. Day, PharmD, RPh
Director of Pharmacy Consulting
PCCA
Historical Use of Quinacrine

• Approved by FDA in 1964
  • Injectable form for treatment of ascites
  • Oral tablets discontinued by manufacturer in 1994/95
    • Typical oral dose was 100 – 200mg daily, anti-infective indications
    • See PDR 1995 (Atabrine®)
  • Commercial Triquin® (Winthrop) tablet available in late 50’s to early 70’s (1972). See PDR 1961
    • Combo of Quinacrine, Chloroquine and Hydroxychloroquine
    • Used for Lupus (chronic discoid lupus erythematosus)
  • Injectable discontinued in 1977
Quinacrine HCl USP

- USP monograph first appeared in 1942 (USP XII), but was removed in 1995 (USP 23 – NF 18) once commercial product discontinued
  - Small market size, economics do not support manufacturing costs

Quinacrine HCl from PCCA meets specifications from USP 22 and 1980 BP
DESCRIPTION
Each tablet contains 100 mg of quinacrine hydrochloride, a bright yellow, odorless, bitter crystalline powder that is water soluble (1:35). Inactive Ingredients: Pharmaceutical Glaze, Starch, Stearic Acid, Talc.

ACTION
TRIQUIN® contains certain trivalent mesoquinones, for example, leuco triquin® (active isomer), pseudoverdolin® (quinacrine) and auro triquin® (mesoquinone) derived from the quinine alkaloids. It is thought to exert its action through interaction with the phospholipid bilayer of the erythrocyte membrane, and by inducing aggregation and agglutination of all forms of malaria.

INDICATIONS
TRIQUIN® is indicated for the prophylaxis and treatment of malaria infections caused by susceptible strains of P. falciparum, P. vivax, P. malariae, and P. ovale. It is not effective against P. falciparum infections caused by chloroquine-resistant strains.

ADVERSE REACTIONS
TRIQUIN® may cause gastrointestinal side effects such as nausea, vomiting, and diarrhea. Other possible side effects include dizziness, headache, and skin rash.

DOSE AND ADMINISTRATION
Adults: Start with one tablet daily for 10 days followed by four tablets once weekly. Children: Start with one tablet daily and increase to two tablets daily after 10 days.

COMPOSITION:
TRIQUIN® contains Atabrine® hydrochloride 25 mg, Aralen® phosphate 65 mg, and Plaquenil® sulfate 50 mg per tablet.

ACTION AND USES:
TRIQUIN® is indicated for the prophylaxis and treatment of malaria infections caused by susceptible strains of P. falciparum, P. vivax, P. malariae, and P. ovale. It is not effective against P. falciparum infections caused by chloroquine-resistant strains.

ADMINISTRATION AND DOSAGE:
Adults: One tablet daily for 10 days followed by four tablets once weekly. Children: One tablet daily and increase to two tablets daily after 10 days.

SIDE EFFECTS:
TRIQUIN® may cause gastrointestinal side effects such as nausea, vomiting, and diarrhea. Other possible side effects include dizziness, headache, and skin rash.

PRECAUTIONS:
Use caution in patients with hepatic or renal impairment. Monitor patients for signs of liver or kidney toxicity.

TRIQUIN® (tri' kwinn)
COMPOSITION: Atabrine® hydrochloride 25 mg, Aralen® phosphate 65 mg, and Plaquenil® sulfate 50 mg per tablet.

ACTION AND USES: For chronic discoid lupus erythematosus, light-sensitivity eruptions, and solar urticaria.

ADMINISTRATION AND DOSAGE: Adult dose, 1 to 2 tablets 2 to 4 times daily reduced gradually until a maintenance dose is determined.

SIDE EFFECTS: Headache, visual disturbances, gastrointestinal complaints, dermatitis, dizziness, leukenia may occur.

SIDE EFFECTS usually regress on reduction of dosage or discontinuance of product.

PRECAUTIONS: Use with caution in patients with hepatic or renal impairment. Monitor patients for signs of liver or kidney toxicity.

This product information was prepared September 18, 2000.
American Drug Index, 1972

Meth-Dia-Mol Sulphonamide,
See: Neomycin, Prep. (Lilly)
W/Fentanyl.
See: Meth-Dia-Mol
TRIPLE VITAMIN FORTE. (Sav-O-Med) Vit. B-6 100 mg., B-1 100 mg., B-12 100 mcg./cc.
Vial 10 cc.
TRIFEROL-S. (Spaner) Testosterone 100 mg., estrone 5 mg., progesterone 25 mg./cc.
Vial 10 cc.
TRIPOTTASSIUM CITRATE, N. F. XIII.
See: Potassium Citrate.
TRIPRILONINE HCL. N. F. XIII. Trans-4-
methyl-phenyl-1-(2-pyridyl)-3-pyrrolidino-propi-
none HCl. Trans-2-[3-(1-pyridinyl)-1(0-tolyl)
propenyl]pyridine hydrochloride. (E)-2-[(3-1-Pyr-
olidinyl)]-1-propenyl)propenylpyridine monohy-
drochloride. Tab., N. F. XIII.
See: Actinic (Boroughs Wholesale)
W/Codeine phosphate, pseudophedrine HCl, glycercyl glucoside.
See: Actinic-C. Syr. (Boroughs Wholesale)
TRIPAL. (Century) Sulfadiazine 100 mg., sulfa-
metazine 50 mg., sulfacetamide 100 mcg./Tab.
Tab.: 100's, 300's. Supp. 1 pt., cc.
Use: Triple sulfonamide therapy.
TRIPROTEIN. (Schering) Syr. Glutacline. Vial 2 gm.
TRIPTIL HYDROCHLORIDE (Watt & Sharp & Dohme) Propylidynyl hydrochloride,
Use: Antidepressant.
TRIFEROL. (Commerz) Scopolamine hydrobromide
0.25 mg./Cap. Bot. 15s.
Use: Motion sickness.
TRICIN. (Winthrop) Quinidine (Atabrine HCl)
25 mg., chlorothiazide (Aralen PG) 65 mg., hydro-
xychloroquine (Plaquenil) 50 mg./Tab. Bot. 100s,
Use: Diuretic.
TRIGONINI. (First Aid) Neomycin (Aristane HCl)
25 mg., chloroquine (Aralen PG) 65 mg., hydro-
xychloroquine (Plaquenil) 50 mg./Tab. Bot. 100s,
Use: Antimicrobial.

*Generic name: approved by FD A or recognized
as USAN or by U. S. P., N. F. or N. O.
Clinical Utilization

• Today, in compounding, majority of compounds dispensed are for patients with Lupus
  • Most commonly combined with hydroxychloroquine (HC) to reduce dose (and dose-related toxicities) of HC

• Highlights from a recent international LUPUS meeting highlighted a proposed combination of low dose hydroxychloroquine + quinacrine HCl for long term maintenance of SLE
  • Reduction of risk of ocular toxicity by HC by utilization of lower dosing – due to synergy with quinacrine.
A highlight from the LUPUS 2014 meeting: eight great ideas
Clinical Utilization

- Detailed review article written in 1989 by Dr. Daniel J. Wallace (The Use of Quinacrine (Atabrine) in Rheumatic Diseases: A Reexamination, Seminar in Arthritis and Rheumatism 1989; 18: 282-96)
  - Details pharmacologic effects of Quinacrine
  - Reviews safety
  - Focused on utilization in patients with Lupus
  - Provides recommendations on use in Lupus
Lupus trials
771 total patients, 73% average response rate

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<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Excellent*</th>
<th>Improved*</th>
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Totals (N) 771 209 352 210
Totals (%) 100 27 46 27

*Excellent or improved response, 73%.

### Table 4. Atabrine v Plaquenil in Lupus: A Comparison

<table>
<thead>
<tr>
<th>Advantages of Atabrine</th>
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<tbody>
<tr>
<td>No retinal toxicity</td>
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<tr>
<td>Initial dose: one tablet/day</td>
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<tr>
<td>Onset of action in 2 to 4 weeks</td>
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<tr>
<td>Promotes energy; decreases fatigue</td>
<td></td>
</tr>
<tr>
<td>Disadvantages of Atabrine</td>
<td></td>
</tr>
<tr>
<td>Greater skin toxicity</td>
<td></td>
</tr>
<tr>
<td>Greater gastrointestinal symptoms</td>
<td></td>
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<tr>
<td>1/50,000 chance of aplastic anemia</td>
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<table>
<thead>
<tr>
<th>Advantages of Plaquenil</th>
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<tbody>
<tr>
<td>FDA-approved for lupus</td>
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</tr>
<tr>
<td>Greater activity against synovitis</td>
<td></td>
</tr>
<tr>
<td>Little skin or gastrointestinal toxicity</td>
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<table>
<thead>
<tr>
<th>Disadvantages of Plaquenil</th>
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<tr>
<td>2- to 4-month onset of action</td>
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<tr>
<td>Retinal toxicity</td>
<td></td>
</tr>
<tr>
<td>Not as powerful in vitro as Atabrine</td>
<td></td>
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</table>

<table>
<thead>
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<th>Advantages of both</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented synergy when administered together</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5. How to Use Atabrine and Maximize Its Effectiveness and Safety in Lupus

1. Never exceed doses of 100 mg daily.
2. If optimal effects achieved after 3 to 6 months, begin tapering drug by one day a week every 2 months. Maintain at 1 to 3 tablets a week for 3 to 5 years.
3. If optimal effects not achieved, add Plaquenil (or vice versa).
4. Discontinue if (a) no effect is seen after 8 weeks, (b) a lichen planus skin rash occurs, (c) significant drop in hemoglobin and reticulocyte counts are observed.
5. Adverse gastrointestinal or pigment reactions can be ameliorated by decreasing the dose to ≤50 mg daily. The drug takes longer to work under these circumstances.
6. If CBCs are obtained every 2 to 3 months and the above guidelines are followed, the incidence of aplastic anemia is 1/500,000.
7. Atabrine can improve symptoms and signs of fever, adenopathy, discoid lupus, sun sensitivity, mucous membrane lesions, alopecia, arthritis, headache, fatigue, and serositis.
8. Atabrine has no activity against nephritis, myocarditis, CNS, hematologic, hepatitis, or lung parenchymal involvement of lupus.
The benefit of combining hydroxychloroquine with quinacrine in the treatment of SLE patients

**Introduction**

Quinine and its derivatives were already successfully used in the management of cutaneous LE around the turn of the 19th century. In 1943 the newly synthesized quinacrine (Qn, also known as mequinine) was designated as the effective antimalarial prophylactic treatment in the southwest Pacific theater of war, where it was taken daily for 3 years by three million American soldiers. Later it was noticed that soldiers suffering from SLE or rheumatic arthritis improved while maintained on Qn. In the 1950s antimalarial drugs [such as: chloroquine (CQ); Qn; hydroxychloroquine (HQC); amodiaquine] were gradually introduced into the treatment of SLE. The combination of CQ and Qn was noted to result in an improved anti-inflammatory effect, leading to the manufacture of ‘triquine’ (i.e. a mixture of CQ+Qn+HQC). This was later withdrawn due to the general avoidance of antimalarials when high doses of some of these drugs were given, severe side effects (agranulocytosis, eye toxicity, etc.) were noted, which tempered the earlier enthusiasm. However, HQC, when used properly, proved to be safe and its administration in SLE patients was continued, especially after the published report by the Canadian HQC study group, which demonstrated that its discontinuation was associated with exacerbation of the disease. Furthermore, its synergistic/additive effect with cyclophosphamide, methotrexate (MTX) and cyclosporin-A was described in several
Response to Antimalarials in Cutaneous Lupus Erythematosus
A Prospective Analysis

Aileen Y. Chang, BA1,2, Evan W. Piette, BS1,2, Kristen P. Foerling, BS1,2,3, Thomas R. Tenhave, PhD, MPH4, Joyce Okawa, RN1,2, and Victoria P. Werth, MD1,2
Aileen Y. Chang: aileench@mail.med.upenn.edu; Evan W. Piette: epiette@mail.med.upenn.edu; Kristen P. Foerling: foerlingk@mail.med.upenn.edu; Thomas R. Tenhave: ttenhave@mail.med.upenn.edu; Joyce Okawa: Joyce.Okawa@uphs.upenn.edu
1Philadelphia Veterans Affairs Medical Center, Philadelphia, PA, USA
2Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
3Institute for Translational Medicine and Therapeutics, University of Pennsylvania, Philadelphia, PA, USA
4Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA, USA

Results—Of 11 patients initiated on hydroxychloroquine, 55% were responders with a decrease in median (interquartile range) activity score from 8.0 (3.5-13) to 3.0 (1.8-7.3) (p=0.03). Of 15 patients who had failed hydroxychloroquine, 67% were responders to initiation of hydroxychloroquine-quinacrine, with a decrease in median (interquartile range) activity score from 6.0 (4.8-8.3) to 3.0 (0.75-5.0) (p=0.004). Nine out of 21 patients (43%) continued on hydroxychloroquine and 9 out of 21 patients (43%) continued on hydroxychloroquine-quinacrine
UK Utilization

- Number of prescriptions in UK’s national health system’s (NHS) database for primary care setting:

<table>
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<th>Period</th>
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<tr>
<td>March to June 2015</td>
<td></td>
<td>806</td>
</tr>
<tr>
<td>Jan to March 2015</td>
<td></td>
<td>997</td>
</tr>
<tr>
<td>Sept to Dec 2014</td>
<td></td>
<td>1,043</td>
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<tr>
<td>July to Sept 2014</td>
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Does not include hospital, private prescriptions, Scotland, Ireland and Wales prescribing
When using a Drug Analysis Print, you should remember that:

- The likelihood of experiencing an adverse drug reaction when taking a medicine cannot be estimated from the information in Drug Analysis Prints. This is because we have limited information about how many people have taken the medicine without experiencing a reaction.
- Reporters are asked to submit Yellow Card reports even if they only have a suspicion that the medicine may have caused the adverse drug reaction. The existence of an adverse drug reaction report on a Drug Analysis Print does not necessarily mean that the medicine has caused the reaction.
- It may be difficult to tell the difference between something that has occurred naturally and an adverse drug reaction. Sometimes reactions can be part of the condition being treated rather than being caused by a medicine.
- Many factors have to be considered when assessing whether a medicine has caused a reported adverse drug reaction. When monitoring the safety of medicines, MHRA staff carry out careful analysis of these factors.
- It is not possible to compare the risks of different medicines by comparing the numbers presented in Drug Analysis Prints.
Taking mepacrine for your systemic lupus erythematosus (SLE)

This information sheet has been given to you to help answer some of the questions you may have about taking mepacrine to treat your systemic lupus erythematosus (SLE). If you have any questions or concerns, please do not hesitate to speak to a doctor or nurse caring for you.

What is mepacrine?

Mepacrine was first introduced in the 1930s as a treatment for malaria. It is one of several antimalarial drugs that have also been found to have anti-inflammatory properties. These properties can help various conditions that cause skin inflammation, including SLE.

Mepacrine is unlicensed in the United Kingdom. This is because the numbers of patients taking mepacrine are very small and it is not cost effective for large pharmaceutical companies to manufacture. As a result mepacrine is made especially for the small numbers of patients who need it by a company called Boots Manufacturing.

Although mepacrine is unlicensed, the Lupus Unit at St Thomas’ has used it safely for many years.

How do I take the medicine?

Doses vary from person to person and your doctor will advise you about your dose. The dose may be as small as 50mg (half a 100mg tablet) taken three times a week. A maximum dose would 100mg taken three times a day.

You may find the tablets taste bitter. It may take several weeks to reach its full effect so you may not experience benefit immediately but it is important to keep on taking your mepacrine.

Which conditions are treated with mepacrine?

SLE causes inflammation in different parts of the body. Mepacrine cannot be used for all types of lupus and is used particularly to treat lupus which causes skin inflammation, such as:

- Discoid lupus erythematosus – causes a rash with inflammation and scarring. Usually found on the face, ears, and scalp and sometimes on other areas.
- Subacute cutaneous lupus erythematosus – causes scaly patches on the skin. Usually found on sun-exposed areas such as the neckline or the forearms, but not the face.

For more information about SLE contact your Consultant, Specialist Nurse or visit the official St Thomas’ Lupus Trust website www.lupus.org.uk.
More UK info

Which skin conditions are treated with mepacrine?

Mepacrine is used particularly to treat discoid lupus erythematosus and for subacute cutaneous lupus erythematosus. Mepacrine has also been used in the treatment of erythema multiforme, sarcoidosis and dermatomyositis (please see the relevant BAD Patient Information Leaflets).

What dose of mepacrine should I take?

Your doctor will advise you about this. For skin conditions, the dose may be as small as 50 mg (half a 100 mg tablet) taken three times a week. A maximum dose would be 100 mg, taken three times a day. The dose for children is 2 mg per kg bodyweight, given as a split dosage three times a day (to a maximum of 300 mg daily). It may take several weeks to reach its full effect.
Lupus erythematosus (Latest modification: 27-Aug-2010)

Mepacrine may be added to the treatment regimen of patients with some forms of cutaneous lupus erythematosus. Treatment is usually started with hydroxychloroquine and if no improvement occurs after about 2 months mepacrine is added at an initial dosage of 100 mg daily. If this combination treatment is effective the dose of both drugs may be decreased after 1 month to reduce any adverse effects. Chloroquine may be used as an alternative to hydroxychloroquine and can also be combined with mepacrine. Mepacrine has also been used as monotherapy, in a similar dose, in patients with visual disorders in whom treatment with hydroxychloroquine or chloroquine was considered unsuitable.

Mepacrine has also been used as an alternative to standard treatments in SLE (►). A small study reported that 5 of 6 patients with SLE unresponsive to treatment with hydroxychloroquine plus prednisone and either azathioprine or methotrexate, had complete remission of their disease when mepacrine (100 mg daily) was added to their existing treatment. Other small studies in patients with stable SLE disease found that the addition of mepacrine to their current treatment reduced the SLE disease activity index and lowered serum levels of B lymphocyte activating factor and ant卡リドリン antibody titres in some patients.

(last reviewed 2011-03-03; last modified 2010-08-27)

The most common adverse effects associated with mepacrine are dizziness, headache, and gastrointestinal disturbances such as nausea and vomiting. Reversible yellow discoloration of the skin, conjunctiva, and urine may occur during long-term use or after large doses; blue/black discoloration of the palate and discoloration of the nails have also been reported. Doses such as those used in the treatment of giardiasis may occasionally cause transient acute toxic psychosis. CNS stimulation and convulsions have been reported at high parenteral doses. Retinopathy similar to that seen with chloroquine and chronic dermatoses, including severe exfoliative dermatitis and lichenoid eruptions, have also occurred after prolonged use of mepacrine. Aplastic anaemia has also been reported after long term use, often preceded by such dermatoses. Hepatitis and hepatic necrosis occur rarely.

(last reviewed 2011-03-03; last modified 2009-07-14)
Safety - aplastic anemia risk

- Low doses of quinacrine are suitable for LE
- “After years of activity, the cutaneous lesions will frequently become quiescent.”
Antimalarial Therapy for Lupus Erythematosus: An Apparent Advantage of Quinacrine

Richard L. Zuehlke, M.D., Patrick J. Lillis, M.D., and Ann Tice, M.D.

ABSTRACT: A retrospective study of 26 quinacrine-treated lupus erythematosus patients failed to show evidence of drug-induced ocular changes. Although quinacrine commonly produces minor side effects, such as yellow discoloration of the skin, and may rarely produce very serious side effects, such as aplastic anemia, it appears to produce much less oculotoxicity than does chloroquine.

Many previous studies have stated or implied that quinacrine possesses the same potential for inducing oculotoxicity as chloroquine. In this report, we briefly review antimalarial drugs and their use in the management of lupus erythematosus, and present data suggesting that there is less oculotoxicity associated with quinacrine than with chloroquine.

For approximately 40 years, antimalarial drugs have been used in the treatment of lupus erythematosus (LE). Christiansen compared chloroquine and quinacrine in the treatment of LE. He found clinical improvement of skin lesions in 89% of 137 patients taking 250 to 750 mg of chloroquine daily. Improvement was visible in 72% of 97 patients taking quinacrine. The dose of quinacrine was lower (usually 100–300 mg daily).

Chloroquine

The use of chloroquine is limited by its oculotoxicity. Although damage to the retina is of greatest concern, other portions of the eye may also be adversely affected.

Corneal deposits of chloroquine can be found in about one-half of chloroquine-treated patients. These deposits are thought to be related to the toxic effects of chloroquine on the corneal epithelium. Some patients may develop corneal opacities, which can be progressive. The corneal changes are usually reversible after discontinuation of chloroquine therapy.

Impairment of ciliary body function can also develop as a side effect of chloroquine therapy. It produces difficulty in changing the distance of focus. This disturbance of accommodation is dose-related and reversible.

Lens opacities in some persons taking chloroquine have been reported. They are described as tiny white flakes in the posterior subcapsular region. These cataracts do not seem to progress or produce significant visual loss. Presently, there is no conclusive evidence of a causal relationship between chloroquine and these lens opacities.

The earliest changes in the retina may be asymptomatic, and are occasionally reversible. At this stage, there is mild pigment stippling or mottling of the macula and loss of the foveolar reflex.

With more advanced retinal change, visual symptoms are usually present. The most common of these are reading difficulties (missing words or letters), photophobia, blurred distance vision, and visual field defects. Funduscopy in patients with more advanced retinopathy shows a hyperpigmented macula, which is surrounded by alternating rings of hypopigmentation and hyperpigmentation. The overall pattern is therefore similar to a target, and has been referred to as a "bull's-eye" appearance.
FDA Briefing – aplastic anemia risk

• 1 case / 500,000 patients
• 0.0002%

ranging from 0.1-0.4% of patients (Lidz et al., 1946; Gaskill et al., 1945). Although rare, the most serious potential toxicity associated with quinacrine HCl is aplastic anemia, which was observed at a rate of between 0.66-2.84 cases/100,000 soldiers treated with quinacrine HCl during World War II (Gonzalez-Sixto et al., 2010; Custer 1946; Palmer et al., 1953; Paton et al., 1955). One third of these cases were determined to be due to quinacrine HCl overdose or concomitant drugs known to be associated with aplastic anemia. Approximately 70% of the remaining cases were associated with patients presenting with lichenoid tissue reactions several months prior to the onset of aplastic anemia. Therefore, the rate of aplastic anemia in patients treated with quinacrine HCl who did not present with a lichenoid reaction is approximately 1 case/500,000 patients (Wallace 1994).
Treatment of Cutaneous Lupus Erythematosus
Review and Assessment of Treatment Benefits Based on Oxford Centre for Evidence-based Medicine Criteria

*R.R. WINKELMANN, BM, MS-IV; *GRACE K. KIM, DO; *JAMES Q. DEL ROSSO, DO
*Ohio University Heritage College of Osteopathic Medicine, Athens, Ohio; *Valley Hospital Medical Center, Las Vegas, Nevada; *Valley Hospital Medical Center, Las Vegas, Nevada; *Touro University College of Osteopathic Medicine, Henderson, Nevada; Las Vegas Skin and Cancer Clinics, Henderson, Nevada
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<tr>
<td></td>
<td>Sunscreen (SPF &gt;50)</td>
<td></td>
<td></td>
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<tr>
<td>TOPICAL TREATMENT</td>
<td>Corticosteroids</td>
<td>Tacrolimus</td>
<td>Pulsed dye laser</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pimecrolimus</td>
<td>Cryotherapy</td>
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<tr>
<td></td>
<td></td>
<td>R-salbutamol</td>
<td>Phototherapy</td>
</tr>
<tr>
<td></td>
<td>Hydroxychloroquine</td>
<td>Retinoids</td>
<td>Azathioprine</td>
</tr>
<tr>
<td></td>
<td>Chloroquine</td>
<td>Methotrexate</td>
<td>Clofazimine</td>
</tr>
<tr>
<td>SYSTEMIC TREATMENT</td>
<td>n/a</td>
<td>Dapsone</td>
<td>Lenalidomide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mycophenolate mofetil</td>
<td>IV/G</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quinacrine</td>
<td>Rituximab</td>
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<tr>
<td></td>
<td></td>
<td>Corticosteroids</td>
<td>Tocilizumab</td>
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<tr>
<td></td>
<td></td>
<td>Thalidomide</td>
<td>Anti-CD4 antibody</td>
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<tr>
<td></td>
<td></td>
<td>n/a</td>
<td>Cefuroxime axetil</td>
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<td></td>
<td></td>
<td></td>
<td>Extracorporeal photopheresis</td>
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<td></td>
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<td></td>
<td>Danazol</td>
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</tbody>
</table>
Recent studies show that combination therapy of HQ or CQ with quinacrine, which has no retinal toxicity, has synergistic efficacy without an increased risk of retinopathy.\textsuperscript{61-64} The synergistic effects of combination therapy have also been reported for patients on HQ or CQ in combination with calcineurin inhibitors, methotrexate, dapsone, and mycophenolate mofetil (Table 2).\textsuperscript{65-68} More studies are needed to examine the use of combination therapy in CLE therapy. Currently, 100mg/day quinacrine is advised as an adjuvant to HQ and CQ in patients with refractory disease or as monotherapy in patients with ocular alterations or other contraindications to HQ or CQ.\textsuperscript{69}

Despite recommendations in the literature for routine laboratory evaluation of patients on antimalarial therapy, this has not been shown to be a particularly cost-effective measure.\textsuperscript{17} However, due to the risks of retinopathy, approval from an ophthalmologist is recommended prior to initiating therapy. Patients taking antimalarials should be advised that the drugs take several weeks to achieve full effects (4–6 weeks for HQ and CQ, 6–8 weeks for quinacrine) and stay in the tissue for several months following drug cessation.\textsuperscript{70} Smokers have decreased response to antimalarial therapy.\textsuperscript{71-73} Therefore, smoking cessation is advised for all CLE patients and especially those receiving antimalarial therapy.
**Fig 1.** Algorithm of treatment for cutaneous lupus erythematosus (CLE). ¹Systemic treatment is usually initiated with hydroxychloroquine (HCQ), if no response, chloroquine (CQ) can be used. ²If there is partial response with quinacrine, methotrexate (MTX) may be used; if there is no response with antimalarials, these drugs are discontinued and MTX is started. ³Retinoids are primarily used in hypertrophic discoid lupus erythematosus (LE), refractory subacute CLE (SCLE) and CLE/lichen planus overlap (discontinue MTX). ⁴Thalidomide should only be applied in severe refractory CLE as remission-inducing agent (discontinue MTX). ⁵Dapsone is recommended for urticarial vasculitis, LE panniculitis, SCLE, and oral ulcers (discontinue MTX). ⁶Mycophenolate mofetil (MMF) or mycophenolate sodium (EC-MPS) is primarily indicated in refractory SCLE (discontinue MTX). ⁷Note that “maintain” only refers to a certain period of time depending on agent, efficacy, and CLE subtype. After clearing of skin lesions, agents should be reduced to minimum effective dose or discontinued; however, sunscreens should be used for prevention of skin lesions. CI, Calcineurin inhibitors; CS, corticosteroids.
FDA concerns – Safety / Toxicity

• DAIP analysis:
  • DNA intercalator and potential mutagen
    • “because mutations can lead to carcinogenicity, many mutagens are considered potentially tumorigenic.”

• References:
FDA concerns - DAIP

“Literature references indicate quinacrine HCl is mutagenic, as discussed further below, and clastogenic in vitro. The identified potential impurities are also possible genotoxins and mutagens (Rotival, 2011; Clarke et al., 2001).” (DAIP)

• Rotival, 2011: “Additionally, using computational approaches, the analysis of the potential toxicity of the impurities compared with the parent compound one shows that ketone and derivatives may exhibit specific toxicity profiles.”

• These conclusions are purely speculative. FDA presents no in vitro or in vivo data to show the presence or effect of the potential impurities.
FDA concerns - DAIP

Further deficiencies of the “potential impurity” analysis
• PCCA required assay is ≥99%
FDA concerns - DAIP

Further deficiencies of the “potential impurity” analysis

• PCCA required assay is ≥99%
• The major degradation products of quinacrine found in Rotival, 2011 are generated from extreme stress with the quinacrine in an aqueous medium.
  • Quinacrine is compounded in anhydrous dosage forms
• Degradation impurities with dry quinacrine powder were not generated until it was heated to about 250 degrees Celsius.
  • This temperature is far beyond any temperature that the powder is ever going to be subject to in compounding or storage of the compounded product.
FDA concerns - DAIP

“Literature references indicate quinacrine HCl is mutagenic, as discussed further below, and clastogenic in vitro. The identified potential impurities are also possible genotoxins and mutagens (Rotival, 2011; Clarke et al., 2001).” (DAIP)

- Clark 2001 examined the mutagenic & carcinogenic potential of quinacrine.
  - *in vitro* study using toxic levels of quinacrine on prokaryotic cells (Salmonella typhimurium) and eukaryotic cells (mouse lymphoma cell line and Chinese hamster ovary cell line)

- Clarke et al. concluded mutagenicity on some of the prokaryotic cell lines
  - Data ignored the antibacterial activity of the substance being tested
Gurova (2009)

Gurova 2009 analyzed Clark 2001 and 174 other studies, as well as conducted their own *in vitro* and *in vivo* experiments.

- Weaknesses of Clark 2001 identified:
  - Prokaryotic (bacteria) cell lines utilized to identify carcinogenic/mutagenic properties, yet quinacrine exerts antibacterial properties.
  - Most tests on eukaryotic cell lines show no carcinogenic or mutagenic effect from quinacrine. Additionally, methodology used in these analyses are considered poor quality and tend to provide false positives for mutagenicity.
  - Modern testing methods for prokaryotic and eukaryotic cells implemented by Gurova show lack of carcinogenicity and mutagenicity.

“Indeed, we found that in vitro treatment of mammalian cells with either 9AA or QC did not result in any signs of DNA damage.”

“We used a number of standard assays for detection of DNA damage and the results of all were clearly negative: no detection of phosphorylation of histone H2AX, no indication of ATM activation and no standard DNA-damage-associated pattern of p53 phosphorylation.”

“Finally, QC did not promote tumor formation in vivo, as would be expected for a genotoxic compound. This experiment was performed in p53+/- mice, which demonstrate a high frequency of radiation-induced tumor formation, and thus are widely used to assess in vivo tumor-promotion/repression.”

“Taken together, these past studies suggest, but do not unequivocally demonstrate, that QC is not genotoxic or mutagenic. However, this position is further supported by our recent experiments (discussed earlier), as well as the history of QC use in humans. Widespread administration of QC to hundreds of thousands of young people for prophylaxis against malaria [16,68], and to women in many different countries for sterilization, had no frequent obvious adverse consequences, including development of cancer [69,70]. Moreover, studies assessing the potential carcinogenic effect of QC (expected to be a direct consequence of a mutagenic effect) showed that QC had no carcinogenic effect on its own (see Table 2 and references therein). In various studies, QC either promoted or reduced the effects of known carcinogens, but in no case was QC found to be carcinogenic itself [71–74].”
FDA concerns - DBRUP

- "Quinacrine HCl is a derivative of acridine, and belongs to a class of compounds that are well known to have mutagenic properties (Ferguson et al., 1991)."
- Ferguson (1991) used *in vitro* prokaryotic methods with the previously described weaknesses.

- DBRUP also cites an intrauterine dosing study (Cancel et al. 2010) which had results of higher incidence of ovarian tumors in a dose dependent manner, most notably at a dose of 70mg/kg in female rats.
  - There was no difference in tumorigenicity from the control in the group dosed with 10mg/kg
  - 10mg/kg is significantly higher than the 100mg PO daily that is recommended for lupus
Safety

- Long history of use, so human tolerances well known
  - Over 80 years of use, millions of patients, well documented antirheumatic uses
  - Generally quite safe, especially when used as per recent lupus protocols
  - 3 million soldiers took for up to 4 years in WWII\(^1\)
    - Mostly minor or reversible SE (HA, dizziness, GI diarrhea) in 50% of patients receiving 100mg daily
    - Lack of retinal toxicity as opposed to HC – major motivator for use.
  - Study of 7,500 US soldiers report 0.4% toxic psychosis, 0.1% CNS toxic cases among 30,000 treated for malaria\(^2\)
  - Most severe is potential for aplastic anemia, but quite low at 0.003% amongst WWII soldiers – blood tests and early signs of rash can prevent
    - 0.0002% per FDA Briefing
  - Study of 120,000 Australian soldiers 1.6% reported rash
    - Yellowish skin stain reported (reversible)
    - Hyperpigmentation of oral mucosa (reversible)
- Carcinogenicity / Tumorigenicity\(^1,2\)
  - Studies were focused on potential use in sterilization (intrauterine)
  - Very high doses in animals (20-30mg/kg), some show anti-tumor properties and others enhanced tumor formation. Conflicting information.
  - LD50 in animals 900mg/kg via oral route

4. Alternative Treatments

Although there are numerous drugs available for treating lupus, the most relevant for this discussion is the antimalarial drug hydroxychloroquine, which is FDA approved for the treatment of lupus and rheumatoid arthritis. Hydroxychloroquine was approved by FDA in 1955 and soon replaced the use of quinacrine HCl. However, quinacrine HCl is still prescribed primarily for the treatment of refractory cutaneous lupus or in conjunction with hydroxychloroquine for systemic lupus erythematosus. The rheumatology community has continually recommended the use of quinacrine HCl for the treatment of lupus, and it is listed as a treatment alternative in the scientific literature, major rheumatology text books, and online medical reference sites.
Conclusions

Millions of people have been treated with multiple doses of quinacrine HCl since the 1940s. Consequently, the safety profile has been well described in the medical literature. The most common adverse reactions involve headache, gastrointestinal symptoms, and yellowing of the skin, which are all reversible by lowering the dosage or discontinuation of the drug. The more serious adverse reactions, which include hepatitis, psychosis, and aplastic anemia, occur rarely and are typically associated with higher doses than the 100 mg/d used to treat rheumatic diseases. Performing a complete blood count and thorough skin exam every three months in quinacrine HCl-treated patients is recommended in the medical literature to screen for potential cases of aplastic anemia. Given the potential benefits of therapy in patients with refractory cutaneous lupus, discussed further below, the safety profile of quinacrine hydrochloride is acceptable considering the relative safety of other lupus treatments.
hydroxychloroquine alone. Three additional studies supporting the use of quinacrine HCl in combination with chloroquine or hydroxychloroquine were referenced in review articles, but were not readily available for independent review (Chung et al., 1997; Feldmann et al., 1994; Von Schmiedeberg et al., 2000). In 1996, the American Academy of Dermatology included quinacrine hydrochloride (100 to 200mg/d) on a list of first-line system treatments for lupus (Guidelines of Care for Cutaneous Lupus Erythematosus, 1996). Most recently, McCune and Gonzalez-Rivera have proposed that the addition of quinacrine HCl to hydroxychloroquine therapy should be seriously considered as long-term maintenance therapy of remission in patients with systemic lupus to reduce ocular toxicity (McCune et al., 2015). Furthermore, the use of quinacrine HCl is recommended in the most-recent algorithm for treatment of systemic lupus erythematosus (Muangchan et al., 2015).
Dermatology (Bologna)

- Standard text for dermatology residents & fellows
## Therapy of Cutaneous Lupus

### Local Therapy
- Sun protection (2)
- Topical and intralesional corticosteroids (2)
- Topical calcineurin inhibitors (2)
- Topical retinoids (3)

### Systemic Antimalarial Therapy
- Hydroxychloroquine (200 mg po qd–bid in adults; up to 6.5 mg/kg ideal body weight/day) (2)
- Chloroquine (125–250 po qd in adults; up to 3.5–4 mg/kg ideal body weight/day) (2)
- Quinacrine (100 mg po qd) (2)
- Combination of hydroxychloroquine or chloroquine and quinacrine (2)

### Systemic Therapy for Antimalarial-Resistant Cutaneous Disease
- Retinoids (e.g., acitretin, isotretinoin) (2)
- Thalidomide (50–100 mg po qd for clearing and, if necessary, 25–50 mg po qd–twice weekly for maintenance) (2)
- Dapsone (primarily for bullous eruption of SLE) (2)
- Immunosuppressive agents (e.g., mycophenolate mofetil, azathioprine) (2)
- Sulfasalazine (2)
- Clofazimine (3)
- Systemic corticosteroids (3)
- Immune response modifiers (e.g., rituximab, abatacept,* belimumab, anti-IL-6 Ab, anti-IL-10 Ab) (3)

*Not more effective than placebo in non-life-threatening SLE.

---

**Adjunctive Therapy**

Sun protection is a vital part of the management of cutaneous lupus. Sun exposure can exacerbate or initiate disease.

Dapsone has been used, but it is associated with a rare subset of bullous eruptions with significant toxicity. In the future, immunomodulators and anti-B-lymphocyte strategies may play an important role.

In patients with systemic lupus erythematosus, particularly those with potentially life-threatening disease, therapy for mild disease includes potent nonsteroidal anti-inflammatory agents and potentially immunosuppressives (e.g., azathioprine and mycophenolate mofetil) that are usually prescribed for a short duration to manage disease flares. In patients with mild degree of major organ involvement, systemic corticosteroids are an alternative to immunosuppressives. For moderate-to-severe disease, immunomodulators and biologics (with the exception of rituximab) are indicated. Combination immunosuppressants are often more effective than monotherapy. For patients with severe or life-threatening disease, the use of cyclophosphamide +/- pulse corticosteroids is effective in inducing remission. For a more detailed discussion, the reader is referred to reference 731.
### Table 3.4 Therapeutic ladder for lupus erythematosus

<table>
<thead>
<tr>
<th>Mild and/or localized disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sunscreens (high SPF with UVA protection) (2)</td>
</tr>
<tr>
<td>- Topical corticosteroids (2)</td>
</tr>
<tr>
<td>- Superpotent topical corticosteroids (2)</td>
</tr>
<tr>
<td>- Topical immunomodulators (e.g., tacrolimus) (3)</td>
</tr>
<tr>
<td>- Intralesional corticosteroids (3)</td>
</tr>
<tr>
<td>- Hydroxychloroquine sulfate (200 mg twice daily) (1)</td>
</tr>
<tr>
<td>- Above plus quinacrine (mepracine) (100 mg/day) (2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extensive/persistent cutaneous disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Oral retinoids (2)</td>
</tr>
<tr>
<td>- Dapsone/sulfapyridine (3)</td>
</tr>
<tr>
<td>- Clofazimine (3)</td>
</tr>
<tr>
<td>- Methotrexate (3)</td>
</tr>
<tr>
<td>- Thalidomide (2)</td>
</tr>
<tr>
<td>- Auranofin (3)</td>
</tr>
<tr>
<td>- Azathioprine (2)</td>
</tr>
</tbody>
</table>

### Systemic disease

- Prednisone (1)
- Azathioprine (1)
- Mycophenolate (2)
- Cyclophosphamide (2)
- Thiopurines, e.g., etanercept
- Cyclosporin A (ciclosporin) (2)
- Interferon (1)
- CD4 monoclonal antibody (3)
- IVIG (2)
- Bone marrow transplant (2)
- Thalidomide (2)
- Leflunomide (Arava®) (2)
- UVA-1 (340-400 nm) (3)

**Key to evidence-based support:** (1) Double-blind; (2) Case series; (3) Anecdotal.

#### Systemic Therapy

Antimalarial therapy has been used for more than a half-century for cutaneous lupus, and it remains the gold standard for systemic therapy. Hydroxychloroquine sulfate is the most commonly chosen antimalarial as it is usually well tolerated. Chloroquine and quinacrine (mepracine) are alternatives. In patients who are not responsive to hydroxychloroquine sulfate, quinacrine may be added to the regimen. Quinacrine may turn the skin yellow, although it does not invariably do so. The dose of hydroxychloroquine sulfate chosen is usually 200 mg once or twice per day. It has been reported that if the dose does not exceed 3.5 mg/kg/day, eye toxicity is quite unlikely.81 However, doses high

where it may be appropriate to use high potency steroids on the face.

Patients should be instructed about the risks and benefits of therapy, need to limit the application to affected areas, and the need for monitoring for cutaneous side effects. Particularly in active discoid lesions, a lupus erythematosus tumidus lesions, intralesional triamcinolone, of given in a concentration of 4-5 mg/mL, can be very effective. The injections may be repeated monthly while the lesions are active. There are anecdotal reports of the use of new topical immunomodulators (e.g., tacrolimus) for facial lesions that are not too thick.

### Systemic Therapy

Antimalarial therapy has been used for more than a half-century for cutaneous lupus, and it remains the gold standard for systemic therapy. Hydroxychloroquine sulfate is the most commonly chosen antimalarial as it is usually well tolerated. Chloroquine and quinacrine (mepracine) are alternatives. In patients who are not responsive to hydroxychloroquine sulfate, quinacrine may be added to the regimen. Quinacrine may turn the skin yellow, although it does not invariably do so. The dose of hydroxychloroquine sulfate chosen is usually 200 mg once or twice per day. It has been reported that if the dose does not exceed 3.5 mg/kg/day, eye toxicity is quite unlikely.81 However, doses high
What We Know

- Dermatomyositis, particularly the cutaneous disease, is often refractory to therapy and can require multiple simultaneous or sequential therapeutic interventions.
- All patients presenting with dermatomyositis skin disease should undergo appropriate investigations for potential concomitant muscle disease, systemic involvement, and/or malignancy.
- Myositis and/or systemic involvement in dermatomyositis is traditionally treated with high-dose systemic corticosteroids plus immunosuppressive agents such as methotrexate, mycophenolate mofetil, azathioprine, or intravenous immunoglobulin, among others.

- Cutaneous disease mandates strict photoprotection and often requires topical corticosteroids. First-line systemic therapy is traditionally hydroxychloroquine. Add-on therapeutic options include quinacrine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin, or thalidomide, among others.
- Most data regarding therapy for cutaneous dermatomyositis is in the form of small case series or retrospective reviews, however, well-designed, multicenter, randomized controlled trials are necessary to better assess the effectiveness of therapeutic options for skin disease in dermatomyositis.

Systemic Treatment Options

First-line (antineoplastics)
- Hydroxychloroquine (Adult: 8.0–8.5 mg/kg ideal body weight/day; Children: ≤5.0 mg/kg ideal body weight/day)
- Chloroquine (Adult: 3.5–4.0 mg/kg ideal body weight/day; Children: ≤3.5 mg/kg ideal body weight/day)

Second-line (these agents may be combined with antineoplastics or used alone)
- Methotrexate (7.5–25 mg/week, orally, IM, SC)
- Mycophenolate mofetil (1000–2000 mg/day)
- Thalidomide (25–100 mg/day)
- Oral retinoids (e.g., acitretin, isotretinoin)
- Dapsone (50–150 mg/day)

Third-line (refractory cases)
- IV Ig (costly)
- Belimumab (not as effective in African-Americans)

Life-threatening or severe inflammatory cutaneous disease (e.g., ASAP/Rowell’s syndrome)
- Systemic CS

Topical immunosuppressive agents: tacrolimus 0.1% ointment or pimecrolimus 1% cream do not cause atrophy, but may be less helpful in very hyperkeratotic lesions.

Systemic therapies targeting the prevention of progression require knowledge of the drugs and specific monitoring.

Antineoplastics (hydroxychloroquine 200 mg twice daily or in combination with quinacrine 100 mg per day) can be employed for cases not adequately treated with topical or local agents.

Systemic retinoids—acitretin 25 to 50 mg p.o. daily, or isotretinoin 40 to 60 mg p.o. daily for 4 months should be considered second-line therapy.

Dapsone (100 to 280 mg p.o. daily), methotrexate, mycophenolate mofetil, and other immunomodulatory agents have also been used. Oral gold also has been reported to be beneficial.

Table 33.6 Suggested therapies for cutaneous lupus should be counseled about daily sun protection and may even lend to exacerbations of systemic disease, and as an adjunct to systemic therapy, is indicated when skin lesions are widespread, or when extracutaneous manifestations are present.
February 29, 2016

Patient: [Redacted]

To Whom It May Concern:

[Redacted] is a patient in Dermatology at Wake Forest Baptist Health. She is being treated for discoid lesions in the setting of chronic cutaneous lupus erythematosus diagnosed in 2000.

At this time we are treating her skin disease with Quinacrine. We had to discontinue the use of Plaqueril due to adverse side effects therefore we switched Ms. [Redacted] to Quinacrine.

We are counting on you to keep this much needed medication available to Ms. [Redacted] and to us Dermatologist so we are able to treat other patients with the same skin condition. If you have any questions or concerns, please feel free to contact my office.

Sincerely,

Joseph L Jorizzo, MD
To Whom it May Concern,

I am an academic dermatologist and heard the disturbing news that the FDA is reviewing the ability of pharmacies to compound quinacrine. This is an extremely important drug that we use in dermatology and rheumatology for our patients with lupus and other autoimmune diseases to help control their disease. It often is used to help decrease the amount of prednisone the patient needs, which is very important as prednisone has many dangerous and irreversible long term side effects. I am part of the Wake Forest Baptist Health Comprehensive Autoimmune Disease clinic which is a regional provider for patients with complex autoimmune disease, and compounded quinacrine is a vital part of our therapeutic armamentarium. Please consider continuing to allow us to use this medication.

Sincerely,

Lindsay C. Strowd, MD
Assistant Professor of Dermatology
Wake Forest Baptist Health
Conclusion

- Compounded as oral capsules for combination therapy in patients with lupus
  - Recommended as first line treatment by AAD
  - Included in treatment algorithms in medical education, protocols, and articles
- Chemically stable, non-mutagenic, non-carcinogenic, non-tumorigenic
- Long history of use in human populations around the world
  - Known adverse reaction profile, well-established guidelines for prescribing, patient counseling, and patient monitoring
  - Very low incidence of adverse reactions at therapeutic dosing
THANK YOU

Questions from the Committee?
Boswellia Serrata Extract

• Boswellia serrata extract (SWSE) is the subject of monographs in the United States Pharmacopeia (USP), European Pharmacopeia (EP) and Chinese Pharmacopeia (CP)

• Has a long and widespread history of use in Chinese medicine as well as in Europe, Africa and the United States

• Available as a herbal dietary supplement (Superior Labs, Swanson, Nature’s Way, Nature’s Answer, Solgar, Now, Himalaya, Pure Encapsulations, etc…)

Safety and adverse effects

- Generally well tolerated
- Animal studies reflect no signs of toxicity or mutagenicity, carcinogenicity has not been reported
- Associated with gastrointestinal adverse effects including diarrhea, abdominal pain and nausea (consistent concern with most NSAIDs)
- Interaction with oral anticoagulant, leading to increased anticoagulant effect (concern with most NSAIDs)
<table>
<thead>
<tr>
<th>Study</th>
<th>design</th>
<th>Therapy length</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double blind, placebo-controlled clinical study - Sengupta et al. (2008)</td>
<td>75 patients with knee OA, randomized to receive 100-250 mg enriched BWSE once daily or placebo</td>
<td>90 days</td>
<td>Statistically significant pain reduction, compared with placebo. Only minor adverse event reported.</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo controlled, crossover study – Kitmmatkar et al. (2003)</td>
<td>30 patients with knee OA 333 mg BWSE 3 times per day</td>
<td>8 weeks</td>
<td>Statistically significant improvement in pain, swelling severity and loss of function of functions compared with placebo</td>
</tr>
<tr>
<td>Double-blind, randomized placebo controlled study – Sengupta et al. (2010)</td>
<td>60 patients with knee OA, randomly assigned to receive 50 mg enriched BWSE twice daily or placebo</td>
<td>90 days</td>
<td>Statistically significant pain reduction, compared with placebo</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo controlled crossover study – Vishal et al. (2011)</td>
<td>60 patients with knee OA, randomized to receive 50 mg twice daily enriched BWSE once daily or placebo</td>
<td>30 days</td>
<td>Statistically significant pain reduction, compared with placebo. Only minor adverse events were reported in both active and placebo groups</td>
</tr>
</tbody>
</table>
# Efficacy data - BWSE

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Therapy length</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, prospective, open-label, comparative trial of BWSE and valdecoxib – Sontakke et al. (2007)</td>
<td>66 patients with knee OA, 10 mg valdecoxib daily or 333 mg BWSE three times daily</td>
<td>6 months – results compared at baseline, and multiple time-points up to 7 months</td>
<td>Statistically significant reductions in pain, stiffness, and function based on Womac subscales favoring valdecoxib at 1 month and BWSE at 7 months. Only minor adverse events reported.</td>
</tr>
<tr>
<td>Randomized, placebo controlled study - Ahangarpour et al. (2014)</td>
<td>60 patients with type 2 diabetes – divided to receive BWSE 900 mg daily or placebo</td>
<td>6 weeks</td>
<td>Significant increase in HDL and decrease in blood cholesterol, LDL, and frucrosamine. No reported adverse effects.</td>
</tr>
<tr>
<td>Open, non-randomized monocentric clinical trial with two parallel treatment groups – Gupta et al. (2000)</td>
<td>30 patients with chronic colitis were given either BWSE 300 mg three times daily or Sulfasalazine 1 g three times daily</td>
<td>6 weeks</td>
<td>Study showed similar results of effectiveness for both treatment and that BWSE could be effective as a treatment for chronic colitis.</td>
</tr>
</tbody>
</table>
Conclusion

- Well tolerated in clinical studies

- Extensive efficacy data to support anti-inflammatory activity

- BWSE is available as a dietary supplement from many vendors without quality verification or monitoring

- Compounding can provide formulations with USP monographed material from FDA registered and inspected facilities, can verify chain of custody and origin
Conclusion

• Compounding pharmacists are able to accurately prepare what the physician requests in a suitable dosage form as needed by individual patients

• BWSE prepared pursuant to a prescription order places the care and monitoring of the patient in the hands of both the physician and pharmacist
Pharmacy Compounding Advisory Committee review of Aloe Vera Freeze-Dried 200:1

March 8, 2016
# Defining Aloe Vera Freeze Dried 200:1

<table>
<thead>
<tr>
<th>Extract Type</th>
<th>Description</th>
</tr>
</thead>
</table>
| Whole leaf extract            | Describes products derived from the entire leaf that were filtered/purified  
• Contains latex and gel  
• Contains **anthraquinones**  
• Aloe USP                                                                                                                                                                                                                                         |
| Decolorized whole leaf extract | Prepared by filtration with activated charcoal, that clarifies the liquid aloe mass  
• Contains residual latex and gel  
• Contains < 10 ppm Aloin (*little to no latex anthraquinones*)                                                                                                                                                                               |
| Aloe latex                    | Brown to yellow-brown, or red sap located between the rind and inner leaf  
• Contains **anthraquinones**  
• Substance is commonly used for laxative purposes                                                                                                                                                                                               |
| Aloe vera gel                 | Liquid derived from the inner leaf  
• Contains gel only  
• Freeze-dried powder Contains < 1 ppm Aloin (*little to no latex anthraquinones*)                                                                                                                                                     |
How Aloe Vera Freez Dried 200:1 is Derived

- Fresh aloe leaves
- Hand removal of outer Part of leaf
- Grinding, enzyme treatment, filtration
- Low temperature vacuum evaporation
- Liquid Concentrate
- Spray Drying with matrix (maltodextrin)

Typical Aloin content <1 ppm (based on industry standard)
Safety

- National Toxicology Program (NTP) report concluded that aloe vera extracts from whole leaf extracts did increase the instance of carcinogenic activity\(^1\)

- In the Central European Journal of Immunology (CEJI) a published study showed feeding mice Aloe vera inner leaf gel with low to no concentrations of anthraquinones had anti-tumor effect\(^2\)

- In another CEJI publication Aloe vera gel fed mice showed stimulation of cell-mediated immunity and antibody production\(^3\)

\(^1\) NTP technical report on the toxicology and carcinogenesis studies of nondecolorized whole leaf extract of Aloe Barbadensis Miller (Aloe Vera) in F344/N rats and B6C3F mice (drinking water study) / National Toxicology Program. 2011.


Safety

- Cosmetic Ingredient Review expert panel concluded that use of inner leaf gel safe for cosmetic use if anthraquinone levels remain under 50 ppm\(^1\)

FDA approved options for wound care

- Santyl® (collagenase) ointment
  - indicated for debriding chronic dermal ulcers and severe burn

- REGRANEX (becaplermin) gel
  - treatment of lower extremity diabetic neuropathic ulcers by stimulating proliferation

WARNING: INCREASED RATE OF MORTALITY SECONDARY TO MALIGNANCY
AN INCREASED RATE OF MORTALITY SECONDARY TO MALIGNANCY WAS OBSERVED IN PATIENTS TREATED WITH 3 OR MORE TUBES OF REGRANEX GEL IN A POSTMARKETING RETROSPECTIVE COHORT STUDY. REGRANEX GEL SHOULD ONLY BE USED WHEN THE BENEFITS CAN BE EXPECTED TO OUTWEIGH THE RISKS. REGRANEX GEL SHOULD BE USED WITH CAUTION IN PATIENTS WITH KNOWN MALIGNANCY.
Retardation of wound healing by silver sulfadiazine is reversed by Aloe vera and nystatin

- Full-thickness wounds were created in Sprague-Dawley rats

- Groups were treated with the following for 14 days:
  - saline control
  - placebo (aqueous cream) control
  - silver sulfadiazine (SSD) cream 1% or SSD 0.5%
  - SSD 1% with Aloe vera
  - SSD 1% with nystatin

- Wound contraction was delayed by saline and SSD groups
- Nystatin and Aloe vera, when added to SSD, reversed effect.

Influence of aloe vera on the healing of dermal wounds in diabetic rats

• Full-thickness wounds on rats were treated either by topical application by oral administration with Aloe vera gel (AVG)

• AVG was prepared using lyophilized or freeze-dried gel only, mixed in water.

• Collagen, hexosamine, total protein, DNA content, rates of wound contraction, epithelialization, and tensile strength measurements were made on treated and untreated wounds

• Results indicated that wound treatment with Aloe vera in diabetic rats may enhance all processes of wound healing including collagen synthesis, and wound contraction

Effect of aloe vera gel to healing of burn wound a clinical and histologic study

- 27 patients with partial thickness burn wound (as the result of flame burn or scalding)

- Treated with aloe vera gel or vaseline gauze

- Aloe vera gel treated lesion healed faster than those treated with vaseline gauze

- The average time of healing was 11.89 days vs. 18.19 days

- Only minor adverse effects observed

Effectiveness of Aloe Vera gel compared with 1% silver sulfadiazine cream as burn wound dressing in second degree burns

- **50 patients** with superficial and partial thickness burns were divided into two equal groups randomly

- Aloe vera gel (AVG) used consisted of unrefined gel taken from the inner leaf

- Aloe Vera gel was compared with 1% silver sulfadiazine (SSD) cream as wound dressing

  - Aloe Vera gel group healed remarkably earlier than 1% SSD group

  - Aloe Vera gel group were relieved of pain earlier than 1% SSD group

Conclusion

- Studies have indicated:
- Aloe vera modulated inflammation\(^1\)
- Increased rate of wound contraction and epithelialization \(^1,2,3,4\)
- Decreased scar tissue size\(^1,2\)
- Increased the organization of the regenerated scar tissue\(^1,2,3\)
- Increased levels of collagen and glycosaminoglycans\(^1\)
- Low to no occurrence of serious adverse effects topically and orally\(^4,5\)

Fagron North America: Nominator

Pharmacy Compounding Advisory Committee review of Ribose

March 8, 2016
D-Ribose

- Aldapentose, monosaccharide (simple sugar). Key backbone of (RNA)

- Central to the formation of adenosine triphosphate (ATP)

- ATP - main energy source for cellular function, dysfunctions of which can be implicated in neuromuscular disease

General use in the market

• Naturally occurring in milk, eggs, meat, vegetables and nuts

• Available as a food additive and dietary supplement (Doctor’s Best, S.H.I.N.E, Jarrow, Now, Source Natural, Life Extension, Dourlas, Well Body, Carlson Labs, Sedona, Hard Rhino, Solgar, etc…)

• Current GRAS notification (Bioenergy Life Science Inc.) accepted by FDA without further question¹

• Subject of a United States Pharmacopeia (USP) dietary monograph

Clinical findings

- Clinical assessment of Ribose in patients with stable coronary artery disease (CAD) showed improved tolerance to ischemia and few serious adverse effects with administration up to 60 g/day.\(^1\)

- In pilot study of 41 patients with fibromyalgia or chronic fatigue syndrome, Ribose was well tolerated at 15 g/day with significant improvements in sleep, energy, mental clarity, pain intensity and well being.\(^2\)

- Significant quality of life improvement was found in a pilot study of 15 patients taking with CAD using Ribose 15g/day.\(^3\)

Safety

- FDA notes – **no significant concerns** regarding animal safety data
- Few to no serious adverse events noted in clinical trials
- A 13 week oral toxicity study conducted in Wister rats concluded **no observed adverse effect levels** (NOAEL)\(^1\)
- Ribose-induced advanced glycation end products (AGEs) in glycation of proteins and possible cognitive impairment with excess doses in mice \(^2,3\)
- Asymptomatic hypoglycemia is observed at statistically insignificant levels and may not be clinically meaningful

Conclusion

• Well tolerated in clinical trials

• Clinical data suggests consistent quality of life improvement with moderate dosing of Ribose

• Ribose is available as a dietary supplement from many vendors without quality verification or monitoring

• Compounding can provide formulations with USP monographed material from FDA registered and inspected facilities, can verify chain of custody and origin
Conclusion

- Compounding pharmacists are able to accurately prepare what the physician requests in a suitable dosage form as needed by individual patients

- Ribose prepared pursuant to a prescription order places the care and monitoring of the patient in the hands of both the physician and pharmacist
ACETYLCARNITINE

Pharmacy Compounding Advisory Committee
March 8-9, 2016

A.J. Day, PharmD, RPh
Director of Pharmacy Consulting
PCCA
“Acetyl-L-carnitine is likely to be stable as a solid. No report on the stability of this compound has been found in the literature. However, its aqueous solution is unlikely to be as stable as its solid form.”

“Given the similarities with acetylcholine, under ordinary storage conditions, acetyl-L-carnitine is likely to be stable when formulated as capsules, but not likely to be as stable when formulated as oral or injectable solutions.”
Published Stability Data

International Journal of Pharmaceutical Compounding
Vol. 16 No. 2 | March/April 2012

Peer Reviewed

Stability of Acetyl-l-carnitine in 5% Dextrose Using a High-performance Liquid Chromatography-Mass Spectrometry Times 2 Method
ABSTRACT

A stability-indicating high-performance liquid chromatography-mass spectrometry times 2 method was developed to establish the stability of acetyl-l-carnitine dissolved in 5% dextrose in water; quantitation of acetyl-l-carnitine and its hydrolysis product l-carnitine was performed using this method. Acetyl-l-carnitine dissolved in water was stress-degraded at a pH range of 3 to 12, and conversion to l-carnitine was quantified over 18 hours. The method was further validated by stressing the acetyl-l-carnitine solution at 68°C, 82°C, and 90°C for up to 10 days, yielding a temperature-dependent hydrolysis rate constant. Acetyl-l-carnitine solutions were stored at 25°C and 4°C to 8°C for 33 days to validate the kinetics prediction. The liquid chromatography-mass spectrometry times 2 method was sensitive and specific, allowing rapid separation and simultaneous quantitation of acetyl-l-carnitine and l-carnitine. Acetyl-l-carnitine dissolved in aqueous solutions is stable at neutral to acidic pH, but unstable at pH >9. After 1 hour storage at room temperature, only 72.6% of acetyl-l-carnitine was left at pH 11 and 4.2% left at pH 12. The kinetics relationship between temperature and rate constant was ln(k) = -8650.1 /T + 20.344 (r² = 0.9851) at pH 5.2. The time required to degrade 15% of acetyl-l-carnitine was estimated to be 38 days at 25°C or 234 days at 8°C, and was confirmed with actual storage stability testing. Acetyl-l-carnitine dissolved in water (pH 5.2) at concentrations of 1 and 10 mg/mL was found stable at room temperature or refrigerated for at least 33 days using the established stability-indicating method. Acetyl-l-carnitine solutions are not stable at basic pH. When reconstituted in water, acetyl-l-carnitine is stable for over 30 days at room temperature or under refrigeration.
**Conclusions:** Acetyl-L-carnitine is a well-characterized small molecule. The compound is likely to be stable as a solid under ordinary storage conditions when kept away from moisture and heat, but may have stability issues when formulated as an aqueous solution. The nominated compound is easily characterized with various analytical techniques and the synthesis of this compound has been well developed.

**USP38-NF33 Chapter 795:**

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**BUD by Type of Formulation**

- **For Nonaqueous Formulations**—The BUD is not later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier.

- **For Water-Containing Oral Formulations**—The BUD is not later than 14 days when stored at controlled cold temperatures.

- **For Water-Containing Topical/Dermal and Mucosal Liquid and Semisolid Formulations**—The BUD is not later than 30 days.
Comparison of the Effects of L-Carnitine and Acetyl-L-Carnitine on Carnitine Levels, Ambulatory Activity, and Oxidative Stress Biomarkers in the Brain of Old Rats

JIANKANG LIU, a, b ELIZABETH HEAD, c HIROHIKO KURATSUNE, d CARL W. COTMAN, c AND BRUCE N. AMES a, b

a Department of Molecular and Cell Biology, University of California, Berkeley, California 94720, USA
b Nutritional Genomics Center, Children’s Hospital Oakland Research Institute, Oakland, California 94609, USA
c Institute for Brain Aging and Dementia, University of California, Irvine, California 92697, USA
d Department of Hematology and Oncology, Osaka University, Osaka 565-0871, Japan

ABSTRACT: L-Carnitine and acetyl-L-carnitine (ALC) are both used to improve mitochondrial function. Although it has been argued that ALC is better than L-carnitine in absorption and activity, there has been no experiment to compare the two compounds at the same dose. In the present experiment, the effects of ALC and L-carnitine on the levels of free, acyl, and total L-carnitine in plasma and brain, rat ambulatory activity, and biomarkers of oxidative stress are investigated. Aged rats (23 months old) were given ALC or L-carnitine at 0.15% in drinking water for 4 weeks. L-Carnitine and ALC were similar in elevating carnitine levels in plasma and brain. Both increased ambulatory activity similarly. However, ALC decreased the lipid peroxidation (malondialdehyde, MDA) in the old rat brain, while L-carnitine did not. ALC decreased the extent of oxidized nucleotides (oxo8dG/oxo8G) immunostaining in the hippocampal CA1 and cortex, while L-carnitine did not. ALC decreased nitrotyrosine immunostaining in the hippocampal CA1 and white matter, while L-carnitine did not. In conclusion, ALC and L-carnitine were similar in increasing ambulatory activity in old rats and elevating carnitine levels in blood and brain. However, ALC was effective, unlike L-carnitine, in decreasing oxidative damage, including MDA, oxo8dG/oxo8G, and nitrotyrosine, in old rat brain. These data suggest that ALC may be a better dietary supplement than L-carnitine.
FIGURE 4. Malondialdehyde (MDA) in young, old, and old rats treated with 0.15% ALCAR or L-carnitine (CARN) in drinking water for 4 weeks. *P < 0.05 vs. young; #P < 0.05 vs. old.
although only significant in the cortex. Old rats treated with 0.15% L-carnitine showed no reduction in age-associated oxo8dG/oxo8G immunoreactivity.
cortex. ALCAR significantly reduced age-associated increases in nitrotyrosine in the white matter, but L-carnitine did not.
ever, only ALC treatment resulted in a decrease in biomarkers of oxidative damage, including lipid peroxidation (MDA), protein oxidation (nitrotyrosine), and oxidative nucleic acid damage (oxo8dG/oxo8G) in the brain of old rats. The concentrations

In conclusion, ALC and L-carnitine increased ambulatory activity similarly in old rats and elevated carnitine levels in old rat blood and brain. However, L-carnitine did not decrease or enhance oxidative damage, while ALC did decrease MDA, nitrotyrosine, and oxo8dG/oxo8G in old rat brain. These data suggest that ALC is a more effective dietary supplement than L-carnitine.
DeGrandis and Minardi (2002) performed a blinded, randomized, placebo-controlled, pharmaceutical-sponsored trial of 333 patients with diabetic neuropathy treated with 2 g/d for 1 year. This trial also showed a modest increase in nerve conduction velocity. The authors themselves put this finding into perspective: “It should be noted that, overall, the absolute magnitude of the treatment-related changes in [nerve conduction velocity] parameters recorded in our study was relatively small.”
+0.1mV). After 12 months of treatment, mean VAS scores for pain were significantly reduced from baseline by 39% in LAC-treated patients (p < 0.0 vs baseline) compared with 8% in placebo recipients. LAC was well tolerated over the study period.

**Conclusions:** LAC was effective and well tolerated in improving neurophysiological parameters and in reducing pain over a 1-year period. LAC is, therefore, a promising treatment option in patients with diabetic neuropathy.
DeGrandis (2002)

Fig. 1. Change from baseline in pain intensity on the visual analogue scale (VAS) after 6 and 12 months of treatment with acetyl-L-carnitine (LAC) [n = 95] versus placebo (n = 104). *p < 0.05, **p < 0.01. p-Values represent comparison with placebo, error bars represent SD.
Acute pain in patients with HIV infection

1. High concentration capsaicin patches, smoking cannabis and lamotrigine are effective in treating neuropathic pain in patients with HIV/AIDS (N) (Level II).

2. Nucleoside reverse transcriptase inhibitor (NRTIs)-induced neuropathic pain in HIV/AIDS patients is treatable with acetyl-L-carnitine (ALCAR) (N) (Level II).

3. HIV/AIDS patients with a history of problematic drug use report higher opioid analgesic use, but also more intense pain (N) (Level III-2).
The use of nucleoside reverse transcriptase inhibitors (NRTIs) can lead to a toxic neuropathy with neuropathic pain. Acetyl-L-carnitine (ALCAR) can provide neurotrophic support of sensory neurones and therefore its use in the setting of NRTI therapy may encourage nerve regeneration and analgesia. IM or oral ALCAR use was safe and well-tolerated and resulted in a reduction of pain intensity compared to placebo (Youle & Osio, 2007 Level II).

Key messages
1. High concentration capsaicin patches, smoking cannabis and lamotrigine are effective in treating neuropathic pain in patients with HIV/AIDS (N) (Level II).
2. Nucleoside reverse transcriptase inhibitor (NRTIs)-induced neuropathic pain in HIV/AIDS patients is treatable with acetyl-L-carnitine (ALCAR) (N) (Level II).
3. HIV/AIDS patients with a history of problematic drug use report higher opioid analgesic use, but also more intense pain (N) (Level III-2).
FDA Briefing Information - ALCAR

available for use. There is no evidence from methodologically sound clinical studies showing the efficacy of ALC for the treatment of disease.

3. Extensive investigation of ALC in large randomized, blinded, and placebo-controlled trials fails to support its efficacy for any of the proposed uses. The disorders included in the nomination are serious medical conditions for which safe and effective treatments are available in the United States.
Acetyl-L-Carnitine Improves Pain, Nerve Regeneration, and Vibratory Perception in Patients With Chronic Diabetic Neuropathy

An analysis of two randomized placebo-controlled trials

RESEARCH DESIGN AND METHODS — Intention-to-treat patients amounted to 1,257 or 93% of enrolled patients. Efficacy end points were sural nerve morphometry, nerve conduction velocities, vibration perception thresholds, clinical symptom scores, and a visual analogue scale for most bothersome symptom, most notably pain. The two studies were evaluated separately and combined.

RESULTS — Data showed significant improvements in sural nerve fiber numbers and regenerating nerve fiber clusters. Nerve conduction velocities and amplitudes did not improve, whereas vibration perception improved in both studies. Pain as the most bothersome symptom showed significant improvement in one study and in the combined cohort taking 1,000 mg ALC.

CONCLUSIONS — These studies demonstrate that ALC treatment is efficacious in alleviating symptoms, particularly pain, and improves nerve fiber regeneration and vibration perception in patients with established diabetic neuropathy.

Diabetes Care 28:96–101, 2005

Sima (2005)

- 1,257 patients, intention-to-treat
- Two randomized, double-blind, placebo-controlled trials
- Each trial was 52 weeks
- Both trials were multi-center
  - 28 U.S. and Canadian centers (U.S.-Canadian Study [UCS])
  - 34 U.S., Canadian, and European centers (U.S.-Canadian-European Study [UCES])

- Enrolling a total of 1,346 patients
  - Men and nonpregnant women between the ages of 18 and 70 years with diabetes for 1 year and an HbA$_1c$ 5.9% were enrolled
  - The differences between U.S. and Canada were small; therefore, the differences between UCS and UCES were mainly due to the European patient cohort in the UCES.
### Table 1—Pain visual analogue scale (UCS, UCES, and pooled cohorts)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>ALC 500 mg t.i.d.</th>
<th>ALC 1,000 mg t.i.d.</th>
<th>ANOVA P value (placebo vs. 500 mg ALC)</th>
<th>ANOVA P value (placebo vs. 1,000 mg ALC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UCS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>48</td>
<td>61</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>50.40 ± 21.88</td>
<td>57.80 ± 25.92</td>
<td>59.94 ± 24.12</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Week 26 change</td>
<td>−10.25 ± 29.45</td>
<td>−17.59 ± 32.53</td>
<td>−23.26 ± 26.33</td>
<td>NS</td>
<td>0.021</td>
</tr>
<tr>
<td>Week 52 change</td>
<td>−9.72 ± 31.12</td>
<td>−13.16 ± 32.64</td>
<td>−25.53 ± 28.75</td>
<td>NS</td>
<td>0.024*</td>
</tr>
<tr>
<td><strong>UCES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>61</td>
<td>43</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>53.21 ± 25.96</td>
<td>48.28 ± 23.30</td>
<td>56.89 ± 26.94</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Week 26 change</td>
<td>−18.93 ± 26.20</td>
<td>−14.21 ± 26.82</td>
<td>−21.92 ± 31.28</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Week 52 change</td>
<td>−14.51 ± 27.49</td>
<td>−11.84 ± 30.80</td>
<td>−21.75 ± 34.58</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Pooled cohorts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>109</td>
<td>104</td>
<td>128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>51.98 ± 24.18</td>
<td>53.86 ± 25.20</td>
<td>58.56 ± 25.38</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Week 26 change</td>
<td>−15.11 ± 27.89</td>
<td>−16.19 ± 30.21</td>
<td>−22.89 ± 28.57</td>
<td>NS</td>
<td>0.031</td>
</tr>
<tr>
<td>Week 52 change</td>
<td>−12.40 ± 29.11</td>
<td>−12.61 ± 31.74</td>
<td>−23.82 ± 31.45</td>
<td>0.025†</td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± SD for the change over baseline in intention-to-treat patients. *Repeated-measures ANOVA overall P value = 0.031. †Repeated-measures ANOVA overall P value = 0.017.
Adverse events
The most common emergent adverse events were pain, paresthesia, and hyperesthesia. Other events included cardiovascular and gastrointestinal symptoms. There were no safety dropouts. There were nine drug-unrelated deaths. Other dropouts were due to withdrawal of consent and protocol violation. In the total population, pain, paresthesia, and hyperesthesia were reported by significantly fewer patients taking 1,000 mg ALC compared with placebo \( (P = 0.026, P = 0.023, \text{ and } P = 0.025, \text{ respectively}) \). This was also numerically less in patients taking 500 mg ALC, but the differences did not reach statistical significance. The incidence of other adverse events did not differ between placebo and patients on an active drug.
Campone (2013)

- Assessed patients with chemo-induced peripheral neuropathy
- Patients with Ovarian Cancer had less grade 3 & 4 peripheral neuropathy
  - Overall neuropathy incidence was not reduced for all patients, yet it was less severe for Ovarian Cancer patients

Conclusion. Administration of ALC with SAG did not result in a significant difference in overall PN incidence compared with a PBO. OC patients in the SAG/ALC arm had a significantly lower incidence of grade 3 or 4 PN compared with OC patients in the SAG/PBO arm. *The Oncologist* 2013;18:1190–1191
Callander (2014)

- Assessed 32 patients with chemo-induced peripheral neuropathy
- ALCAR patients had less Grade 3 or higher neuropathy and lived longer

**Neurotoxicity**

As assessed by the treating physician, six of 19 (32%) receiving BDD developed grade 3/4 neuropathy, primarily sensory with one subject experiencing grade 4 neuropathy. However, in the ALCAR cohort, 2/13 (15%) experienced grade $\geq$3 neurotoxicity, with no patients experiencing treatment emergent grade 4 PN. This difference is not statistically different. Using a score of $>0$ on the FACT-GOG-
### Table 2: Frequencies and percentages of treatment associated toxicities

<table>
<thead>
<tr>
<th></th>
<th>BDD (N = 19)</th>
<th>BDD-A (N = 13)</th>
<th>BDD + BDD-A (N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 3</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>ANC</td>
<td>1 (5)</td>
<td>3 (16)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Platelets</td>
<td>0 (7)</td>
<td>7 (37)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Infection</td>
<td>3 (2)</td>
<td>2 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>6 (32)</td>
<td>0 (0)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (11)</td>
<td>1 (5)</td>
<td>2 (15)</td>
</tr>
</tbody>
</table>
The median number of cycles of therapy delivered was 5 in both cohorts (range 1–8). The median duration of response was 3 months in the BDD cohort versus 10 months in the BDD-A cohort ($p = 0.097$). Median overall survival rate calculated from time of enrollment for the group was 28.3 months (range 0.2–75.3+), with a median overall survival of 22.9 in the BDD cohort and 28.3 in BDD-A cohort ($p = ns$).

treatment emergent neuropathy continues to be an important consideration that limits long-term administration of bortezomib. We attempted to mitigate the incidence and severity of PN through the use of prophylactic acetyl-L-carnitine. Our study suggests that the addition of ALCAR did not eliminate treatment-related PN, although there appeared to be fewer cases of grade 3 or 4 neuropathy among patients receiving the prophylaxis as reported by the treating physicians. However, as measured by validated instruments such as the FACIT-GOG-NTX and the NPI index, the subjects reported increasing levels of neuropathy and continuing fatigue as they continued on study. Given the observed continued high responses to the BDD-A combination, it is clear that the inclusion of this agent in the treatment regimen did not diminish the response rate and ALCAR was very well tolerated. Major limitations of our study include the study’s small subject numbers and that caused by bortezomib. It is also conceivable that the incorporation of ALCAR in bortezomib containing regimens earlier in the treatment course, e.g., for newly diagnosed MM patients, might offer a protective advantage against the development of PN. However, Hershman recently reported
Acetyl-l-carnitine: a pathogenesis based treatment for HIV-associated antiretroviral toxic neuropathy

Andrew M. Hart\textsuperscript{a,d,*}, Andrew D. H. Wilson\textsuperscript{a,*}, Cristina Montovani\textsuperscript{d}, Colette Smith\textsuperscript{b}, Margaret Johnson\textsuperscript{c}, Giorgio Terenghi\textsuperscript{d} and Mike Youle\textsuperscript{c}

ALCAR treatment resulted in significant reduction in neuropathic pain grade experienced by the patients after long-term treatment. However, a randomized controlled trial utilizing a validated visual analogue pain scale is required to demonstrate conclusive symptomatic benefits. Such a trial is now underway to determine the functional effect of ALCAR treatment in preventing ATN. While there was no placebo arm to this study, the natural history of untreated DSP suggests that the continuous and long-term beneficial effects found in this patient cohort resulted from ALCAR treatment.

Although not formally documented, those who stopped ALCAR treatment suffered rapid symptom worsening, including return of dysaesthesiae. ALCAR treatment was well tolerated with no side effects, no adverse events or wound complications.

Source: Hart 2004
Placebo-controlled double-blind randomized trial on the use of L-carnitine, L-acetylcarnitine, or combined L-carnitine and L-acetylcarnitine in men with idiopathic asthenozoospermia

Giancarlo Balercia, M.D., Francesco Regoli, Ph.D., Tatiana Armeni, Ph.D., Aleardo Koverech, M.D., Franco Mantero, M.D., and Marco Boscaro, M.D.

Result(s): Sperm cell motility (total and forward, including kinetic features determined by computer-assisted sperm analysis) increased in patients to whom LAC was administered both alone or in combination with LC; combined LC + LAC therapy led to a significant improvement of straight progressive velocity after 3 months. The total oxyradical scavenging capacity of the semen toward hydroxyl and peroxyl radicals also increased and was positively correlated with the improvement of kinetic features. Patients with lower baseline values of motility and total oxyradical scavenging capacity of the seminal fluid had a significantly higher probability of responding to the treatment.
Forward sperm motility at each time in the four treatment groups: percentage variations with respect to T-1.

Total sperm motility at each time: percentage variations respect to T-1 (Time: $P < 0.001$; LACTX: $P = 0.001$). Group 1: patients treated with L-acetyl-carnitine (LAC), alone or combined. Group 2: patients treated with L-carnitine (LC) or placebo.

Forward sperm motility at each time: percentage variation respect to T-1 (Time: $P<.001$; LACTX: $P=.001$). Group 1: patients treated with l-acetyl-carnitine (LAC), alone or combined. Group 2: patients treated with l-carnitine (LC) or placebo.

Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for ALS

ETTORE BEGHI¹, ELISABETTA PUPILLO¹, VIRGINIO BONITO², PAOLO BUZZI³, CLAUDIA CAPONNETTO⁴, ADRIANO CHIÒ⁵, MASSIMO CORBO⁶, FABIO GIANNINI⁷, MAURIZIO INGHILLERI⁸, VINCENZO LA BELLA⁹, GIANCARLO LOGROSCINO¹⁰, LORENZO LORUSSO¹¹, CHRISTIAN LUNETTA⁶, LETIZIA MAZZINI¹², PAOLO MESSINA¹, GABRIELE MORA¹³, MICHELE PERINI¹⁴, MARIA LIDIA QUADRELLI¹, VINCENZO SILANI¹⁵, ISABELLA L. SIMONE¹⁰, LUCIO TREMOLIZZO¹⁶ AND THE ITALIAN ALS STUDY GROUP*

Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for ALS.


Abstract

Our objective was to assess the effects of acetyl-L-carnitine (ALC) with riluzole on disability and mortality of amyotrophic lateral sclerosis (ALS). Definite/probable ALS patients, 40–70 years of age, duration 6–24 months, self-sufficient (i.e. able to swallow, cut food/handle utensils, and walk), and with forced vital capacity (FVC) >80% entered a pilot double-blind, placebo-controlled, parallel group trial and were followed for 48 weeks. ALC or placebo 3 g/day was added to riluzole 100 mg/day. Primary endpoint: number of patients no longer self-sufficient. Secondary endpoints: changes in ALSFRS-R, MRC, FVC and McGill Quality of Life (QoL) scores. Analysis was made in the intention-to-treat (ITT) and per-protocol (PP) population, completers and completers/compliers (i.e. taking ≥75% of study drug). Forty-two patients received ALC and 40 placebo. In the ITT population, 34 (80.9%) patients receiving ALC and 39 (97.5%) receiving placebo became non-self-sufficient (p = 0.0296). In the PP analysis, percentages were 84.4 and 100.0% (p = 0.0538), respectively. Mean ALSFRS-R scores at 48 weeks were 33.6 (SD 10.4) and 27.6 (9.9) (p = 0.0388), respectively, and mean FVC scores 90.3 (32.6) and 58.6 (31.2) (p = 0.0158), respectively. Median survival was 45 months (ALC) and 22 months (placebo) (p = 0.0176). MRC, QoL and adverse events were similar. In conclusion, ALC may be effective, well-tolerated and safe in ALS. A pivotal phase III trial is needed.
Beghi 2013

Methods

Study design and eligibility criteria

This was a not-for-profit, multicentre, randomized, placebo-controlled, parallel-arm (1:1), pilot phase II trial. Males and females aged 40 through 70 years with definite, probable (laboratory supported) or probable ALS according to the revised El Escorial diagnostic criteria (7) were eligible. Additional requirements were bulbar-onset or spinal-onset ALS with 6–24 months disease duration, satisfactory bulbar and spinal function (score 3+ on the ALS Functional Rating Scale- Revised (ALSFRS-R) (8) for swallowing, cutting food and handling utensils, and walking); satisfactory respiratory function (forced vital capacity, FVC, >80% of predicted); documented progression of symptoms in the last three months; ability to understand, comply with the study requirements, and give written informed consent. Exclusion criteria were familial ALS, antecedent polio infection, other motor neuron diseases (MND),

Treatment plan

All eligible patients were randomized to receive ALC or placebo in addition to riluzole tablets 50 mg b.i.d. Treatment allocation was centrally managed using a computer-generated, permuted block (with a block size of 4), 1:1 randomization scheme. A separate computer-generated randomization list was prepared and sent in sealed envelopes to each centre. Experimental treatment included ALC in powder 500 mg per packet, or an equivalent placebo, supplied by Sigma-Tau Industrie Farmaceutiche Riunite, Pomezia, Italy. The dose was two packets t.i.d. Active treatment and placebo were indistinguishable to sight and taste. Symptomatic and palliative treatments given during the study were permitted and recorded.

All adverse events (AEs) encountered and any serious events were to be recorded using the Coding Symbols for a Thesaurus of Adverse Reaction Terms (11). Severity was graded according to the modified WHO criteria for toxicity (http://www.regsource.com/_Adverse_Event_Reporting/_adverse_event_reporting.html) where applicable.

Compliance was tested by the local investigators, counting unused packages at each follow-up visit.
Table I. Demographic and clinical characteristics of the sample.

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<th>Placebo (40)</th>
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<tr>
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FDA Briefing Information

• “The disorders included in the nomination are serious medical conditions for which safe and effective treatments are available in the United States.”


Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. O’Connor AB¹.

• “However, in cross-sectional studies, many patients continue to have moderate or severe pain and markedly impaired HR-QOL, despite taking medications prescribed for NP.”
THANK YOU

Questions from the Committee?