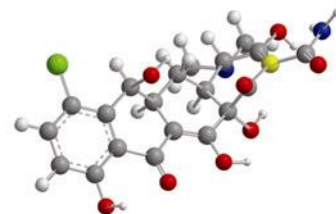


Autoimmunity Research Foundation

Guidance For Physicians

THE MARSHALL PROTOCOL - PHASE ONE



Background

'Marshall Protocol' (MP) is the name given to the therapy which Prof. Trevor Marshall devised based on his discovery that chronic Th1 disease, including much autoimmune disease, is caused by a metagenomic microbiota – a community of intracellular bacteria which lives within the cytoplasm of white cells. The very phagocytes which are supposed to destroy infectious microbes actually become infected by them, and this gives rise to chronic inflammatory disease. A recent peer-reviewed paper describes this pathogenesis in more detail [1].

Direct link to reference 1: <http://AutoimmunityResearch.org/transcripts/AR-Proal-Metagenome.pdf>

Some of Prof Marshall's recent conference presentations can be viewed in order to get a more detailed pathogenic description, for example, his keynote at the 2008 World Gene Congress. The HD video is at URL: <http://www.vimeo.com/2585394> and a written transcript is at URL: http://AutoimmunityResearch.org/transcripts/WCG2008_Keynote_Transcript.pdf.

Additionally, video of his clinical seminar at West China Hospital is at: <http://www.vimeo.com/2599416>

The Phase II clinical trial conducted from 2002-2008 by the Autoimmunity Research Foundation has demonstrated applicability of this antibacterial therapy to a wide range of chronic Th1 immune illnesses [2].

Direct link to reference 2: http://AutoimmunityResearch.org/transcripts/ICA2008_Transcript_TomPerez.pdf

Patients diagnosed with sarcoidosis, post-treatment chronic Lyme syndrome, chronic fatigue syndrome, myalgic encephalomyelitis, uveitis, Hashimoto's thyroiditis, rheumatoid arthritis, fibromyalgia, diabetes, psoriasis, lupus (SLE), multiple sclerosis, and a number of other diagnoses, are all showing satisfactory response when being treated with this antibacterial therapy.

In determining whether a patient can be successfully treated with the MP, a specific chronic disease diagnosis is not as important as the results of D-metabolite blood tests [3], and a therapeutic probe, along with clinical assessment by a knowledgeable health care provider. Short-term evidence of protocol efficacy is provided by the Immunopathology resulting from the therapeutic probe.

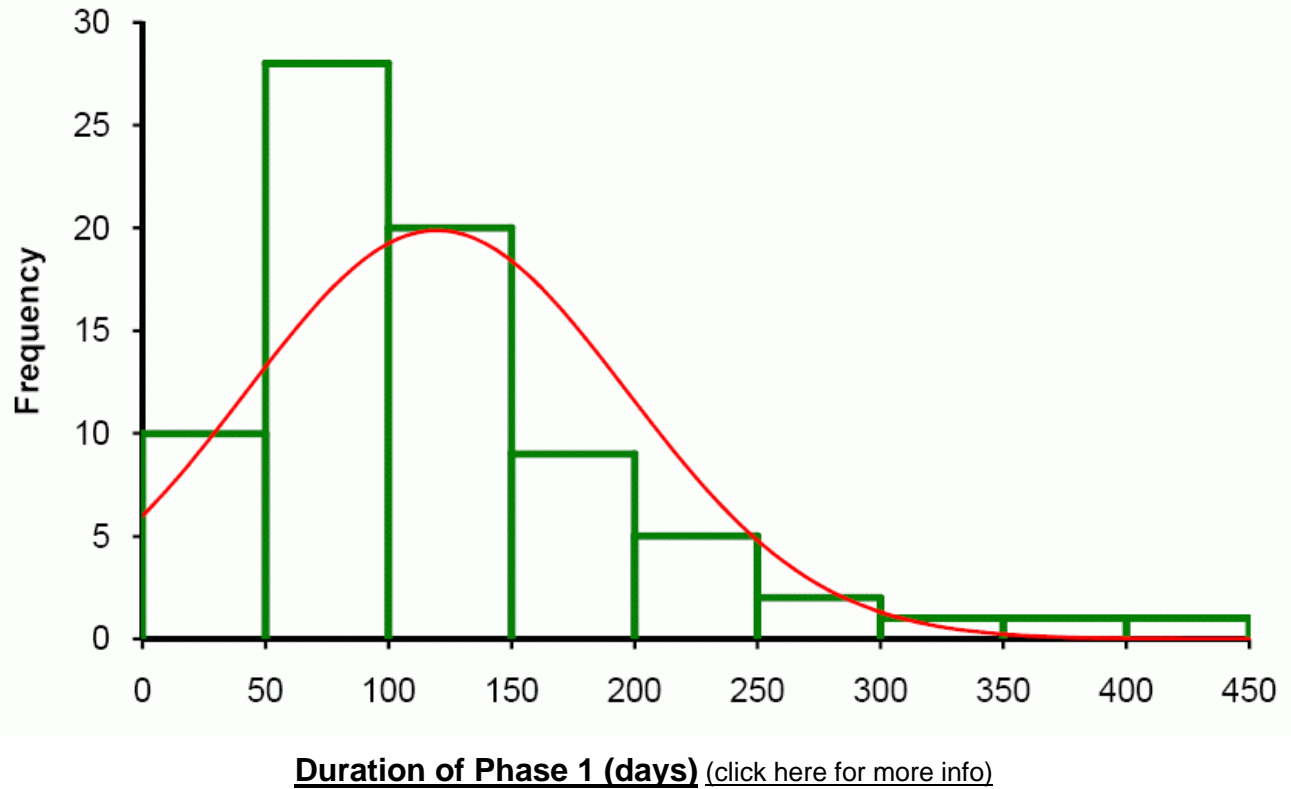
The MP activates the VDR nuclear receptor, which is at the heart of the innate immune system, with a special dosing schedule for the ARB Olmesartan medoxomil (Benicar, Olmecip, Olmetec). Additionally, several pulsed, low-dose, bacteriostatic oral antibiotics are used to trigger the immune system to recognize the pathogens in the metagenomic microbiota. Olmesartan also reduces inflammatory cytokine production by inhibiting the NF kappa-B transcription pathway to inhibit, *inter alia*, the release of TNF-alpha.

The VDR nuclear receptor is activated in healthy individuals by a vitamin D metabolite: 1,25-dihydroxyvitamin-D. The body manufactures all the Vitamin D it needs from 7-dehydrocholesterol, and the immune system works best in the total absence of exogenous steroid. When the operation of the VDR is blocked by ingested Vitamin D, the immune system cannot kill the pathogens and one of the resulting morbidities is chronic disease. That is why avoidance of ingested Vitamin D (in food and supplements) is essential for the innate immune system to function correctly [4,5].

Direct link to reference 5: <http://AutoimmunityResearch.org/transcripts/AR-Albert-VitD.pdf>

Seriously ill patients may develop photosensitivity (symptom increase related to skin and/or eye exposure to sun and/or bright lights) during the healing process, so avoidance of direct and indirect sunlight may be necessary. Patients may need to protect their eyes from bright lights to prevent further retinal damage and reduce neurological symptoms due to, *inter alia*, the effect of ocular 1,25-D production on the brain. Some patients do not experience any significant photosensitivity during recovery, and those who do usually find it more manageable after 12 to 18 months.

A graph showing the observed duration of Phase One, typical of our study cohort, is shown below:



This document covers only the first three to twelve months of therapy. There are two other phases of the MP (see 'Associated Documents' below), as well as the final step to recovery, known as 'Stage 5.' Members are provided access to the Phase Two and Three study site reporting area after completing a progress questionnaire when Phase One has been completed.

Associated Documents

<http://AutoimmunityResearch.org/phase2.pdf>

<http://AutoimmunityResearch.org/stage5.pdf>

<http://AutoimmunityResearch.org/ER.pdf>

<http://AutoimmunityResearch.org/VDR-Time-Benicar.pdf>

Disclaimer

The Autoimmunity Research Foundation will help health care providers understand Th1 inflammatory diseases and the MP, but the responsibility for managing the patient's health and recovery resides with the licensed practitioner. The information in this document is intended to be a guideline for that health care provider.

Health care providers are encouraged to join the 'Private Section for Health Professionals' forum on the MarshallProtocol.com study site to discuss treatment issues with other professionals who are using the MP. They may also contact Dr. Marshall at Trevor.M@yarcnip.com or (818) 584-1201

To ensure success, please encourage your patients to become members of the MarshallProtocol.com study site, to visit (and report) regularly. This site provides additional instructions, helpful hints, and support that will greatly ease a practitioner's emotional support workload, and smooth the patient's path to recovery.

References:

1. Proal, A, Albert P, Marshall TG: Autoimmune disease in the era of the Metagenome. *Autoimmunity Reviews* (in press). Preprint available from URL: <http://AutoimmunityResearch.org/transcripts/AR-Proal-Metagenome.pdf>
2. Waterhouse J, Perez T, Proal A: MP Study Results. *Sixth Intl Congress on Autoimmunity*, Sept 2008. http://AutoimmunityResearch.org/transcripts/ICA2008_Transcript_TomPerez.pdf
Video available from URL: <http://vimeo.com/1789735>
3. Blaney G: Vitamin D Metabolites as Clinical Markers in Autoimmune and Chronic Disease. *Annals of the NY Academy of Sciences*, (in press).
Abstract available: http://mpkb.mp-dev.com/doku.php/home:publications:blaney_annals_2009
4. Waterhouse JC, Marshall TG, Fenter B, Mangin M, Blaney G: High levels of active 1,25-dihydroxyvitamin D despite low levels of the 25-hydroxyvitamin D precursor — Implications of dysregulated vitamin D for diagnosis and treatment of Chronic Disease. *In Vitamin D: New Research*. Volume 1. Edited by: Stoltz VD. New York: Nova Science Publishers; 2006. ISBN: 1-60021-000-7.
5. Albert P, Proal A, Marshall TG: Vitamin D – the Alternate Hypothesis. *Autoimmunity Reviews* (in press). Preprint available from: <http://AutoimmunityResearch.org/transcripts/AR-Albert-VitD.pdf>

===== END OF BACKGROUND =====

Phase One protocol: STEP ONE

Using the lab 'Quest Diagnostics', measure the D-metabolites: 1,25-dihydroxyvitamin-D (1,25-D) and 25-hydroxyvitamin-D (25-D). Remind the drawing lab that the 1,25-D sample must be clotted no more than 30 minutes before centrifuge and the resulting serum must be frozen for shipment. Consult the study site for any alternative testing labs (Quest Diagnostics rigorously insists on frozen serum).

Consult the 'VDR Dysfunction Calculator' for suggestions on interpreting this lab data:

<http://mpkb.mp-dev.com/doku.php/home:tests:vitdinterpretation>

Remember, however, that as the level of 25-D rises above 20ng/ml (usually due to artificial supplementation) the 25-D is providing an immunosuppressive action. It is important to study the analysis from the VDR dysfunction calculator quite carefully. High levels of 1,25-D are suppressed by high levels of 25-D. Consequently, if the D-metabolite tests do not indicate Th1 inflammation but clinical observation suggests Th1 inflammation, a short course of the MP (1 to 2 months) should be used as a therapeutic probe. A longer time period may be needed if 25-D levels remain high, as a therapeutic probe is often not effective unless the 25-D falls below 25ng/ml.

It is helpful (but not necessary) to measure % Lymphocytes, C-Reactive Protein, alkaline phosphatase, triglycerides and serum ACE, to track systemic inflammation. Doctors may want to assess kidney function by testing creatinine or BUN and measure other indicators specific to each patient for a baseline. Lab work (commonly HGB, HCT, creatinine and BUN) may become temporarily abnormal, due to Immunopathology reactions, until the inflammation resolves [4].

STEP TWO

Restrict dietary intake of Vitamin D by eliminating all supplements and foods high in Vitamin D. It is desirable to reduce 25-D to the therapeutic target of less than 12 ng/ml while the patient is going through Phase 1 of the protocol. Retest 25-D every few months to make sure it is dropping toward the lower end of the therapeutic range. Many members of our study cohort have kept their 25-D below 5ng/ml for many years, without any adverse effect.

Note: Patients often begin to feel worse when decreasing light and or D, in the same was as if they were undergoing a therapeutic probe. Therefore, Olmesartan should be prescribed as per step three (below), ready to palliate any resulting immunopathology while the 25-D levels are decreasing.

Photosensitivity

If necessary to avoid the symptoms of photosensitivity, avoid sunlight and bright lights by staying indoors as much as possible and covering up well whenever venturing outside during daylight hours. Very sensitive patients will be less symptomatic if they block natural light in their home or workplace.

Protect eyes from bright lights by wearing amber sunglasses that block infrared rays. Most NoIR, some Bolle100, and some Zeiss models are suitable. For details see the study website:

<http://mpkb.mp-dev.com/doku.php/home:lifestyle:light:noirs>

If photosensitivity is extreme, it may also be necessary to avoid bright indoor lights, even when wearing NoIR glasses. Photosensitive or cautious patients will want to have the glasses on hand before starting Olmesartan.

Many patients report significant symptom resolution just by modifying their light exposure. Patients with severe symptoms may not be able to function without limiting sunlight exposure.

Combining other protocols with the Marshall Protocol is contraindicated

THE FOLLOWING MEDICATIONS AND SUPPLEMENTS ARE CONTRAINDICATED:

1. **Prednisone or cortef.** Antibiotics will not be effective while corticosteroids are suppressing the immune system. Begin or continue the weaning process **with the assistance of palliation from Olmesartan.** ACTH and cortisol production may be monitored to assess adrenal function. See the Knowledge Base article: "*Weaning from Steroids:*"

Direct link to article: <http://mpkb.mp-dev.com/doku.php/home:othertreatments:corticosteroids:weaningoffsteroids>

2. **Immunosuppressants.** These medications will allow occult bacteria to multiply unhindered.
3. **Antibiotics.** Olmesartan greatly potentiates the action of many antibiotics, and consequently a severe or life-threatening Immunopathology may result if non-MP antibiotics are prescribed. The VDR Agonist (Olmesartan) protects vital organs from the cytokine storm, and it must not be withdrawn. If a non-MP antibiotic is temporarily needed for an acute infection, Please follow the instructions in the Emergency Room guidance document:
Direct link to ER document: <http://AutoimmunityResearch.org/ER.pdf>
4. **Antibacterials.** Sulfasalazene, Plaquenil and Methotrexate are antimetabolite antibiotics with actions similar to Bactrim and may produce unwanted or uncontrolled Immunopathology. They **MUST** be discontinued before starting the MP.
5. **Folic acid (Rx or OTC).** Folic acid makes it easier for occult bacteria to replicate and create new DNA. Consuming a balanced diet should provide adequate folic acid.
6. **Thyroid supplements.** Need for these supplements may change within a day or two of starting the Olmesartan blockade. Monitor thyroid function closely and adjust the level of thyroid supplementation downward as needed. (Please see the *Hormonal-interaction Chart* at the end of this document.)
7. **Anticoagulants.** Olmesartan will have a profound effect on the anticoagulant dosing requirement. It is absolutely essential to closely monitor any patient on anticoagulant therapy.
8. **Thiazide diuretics.** Please see the Knowledge Base article

Direct link to 'Diuretics' article: <http://mpkb.mp-dev.com/doku.php/home:othertreatments:diuretics>

9. **Antilipidemics (statins).** There is risk of muscle damage in patients already susceptible to muscle inflammation.
10. **Calcium supplements.** Should be avoided in the presence of hypercalciuria or hypercalcemia. Those without these conditions should generally consume 1000-1500 mg calcium daily, preferably from foods.
11. **Biphosphonates.** May cause calcium deposition into the soft tissues, reduced organ function and possible osteonecrosis of the jaw.
12. **Medications and supplements that are part of another treatment protocol.** Combining palliative protocols with the MP is invariably not successful.
13. **Dietary supplementation and OTC medications.** In general, these are to be avoided because it is not known how they might interact with the medications on the Marshall Protocol, or how they might affect the immune system. Patients taking dietary supplements (and over-the-counter medications) have had a more difficult time adjusting the MP medications. There are a few helpful OTC drugs, and these are discussed in the relevant Forums and Knowledge Base articles.
14. **Progesterone, Estrogen and Testosterone.** The progesterone and androgen nuclear receptors are key components of endogenous antimicrobial expression in the innate immune system. Use of these steroids as supplements, transdermal patches, or IUD, may suppress the immune system

leading to instability and ineffectiveness during MP therapy. The Estrogen-beta receptor expresses the VDR protein itself, and is thus a key component in innate immune homeostasis. If the patient is already on hormone 'replacement' therapy, judicious use of low-dose hormone therapy (to relieve intolerable symptoms) may be necessary until the patient is able to wean from the hormones

A complete discussion of MEDICATIONS TO AVOID can be found at:

<http://www.marshallprotocol.com/forum2/10.html>

Use caution when using the following medications and supplements:

1. **Guaifenesin** is sometimes useful as palliation, and usually effective as an expectorant, for patients on the MP. It is particularly effective in reducing pulmonary, GI tract, and sinus immunopathology. Dose should not exceed 800mg/day. The slow-release formulation can be used.
2. **Quercetin** is sometimes useful as a palliative during the MP, but it must be used with great care. Dose should not exceed 1200mg/day.
3. **Antihypertensives.** May be continued if blood pressure remains high on Olmesartan, but monitor BP, reducing other antihypertensives as soon as practicable. Hypertension often resolves quite quickly. Please note that Diuretics may cause problems. Spironolactone may cause hyperkalemia
Direct link to 'Diuretics' article: <http://mpkb.mp-dev.com/doku.php/home:othertreatments:diuretics>
4. **Hawthorn.** May react negatively with Olmesartan.
5. **Lithium.** Toxicity may occur when taking Olmesartan due to slow renal clearing. Monitor blood levels closely. May slow recovery.
6. **Potassium supplements.** Potassium may become too high due to renal resorption. Monitor Serum K+ if concerned, or in the presence of renal disease.

Oxygen may be used safely at all times, and is the preferred intervention for pulmonary distress. Any patient who experiences shortness of breath should have emergency oxygen supplies on-hand.

STEP THREE

Commence therapy by prescribing pure Olmesartan Medoxomil 40mg every six hours to interrupt the inflammatory cycle and reduce the severity of potential Immunopathology (eg: 6am, noon, 6pm, midnight.) Olmesartan comes in 20mg and 40mg tablets, make sure you prescribe the 40mg tablets.

WARNING: *The FDA recommends patients do not take Olmesartan during pregnancy and/or lactation.*

Olmesartan medoxomil is the only angiotensin receptor blocker (ARB) which activates the patient's immune system. 'No substitutions' should be written on the prescription. Any combination formulation must not be used. Patients should keep several weeks' supply of Olmesartan in reserve to use in case it is needed to treat an intolerable Immunopathology.

Olmesartan is a CRITICAL component of the Marshall Protocol. Without it, the immune system does not fully react when the antibiotics start to kill the bacteria. Patients with chronic disease who just take MP antibiotics, usually do not experience significant immunopathology until they start taking Olmesartan, and if any immunopathology is experienced, it will often be palliated by Olmesartan.

In patients with chronic disease, Olmesartan has two independent modes of action. As an anti-inflammatory, it prevents fibrotic tissues from forming, and reduces the release of inflammatory cytokines. As a Vitamin D Receptor agonist, Olmesartan also activates the innate immune response, including expression of key antimicrobial proteins and peptides. It is the body's own antimicrobials which are key to a full recovery, and become especially important in later stages of recovery:

Direct link to a graphic of the six stages of recovery: <http://AutoimmunityResearch.org/VDR-Time-Benicar.pdf>

Because Olmesartan has strong organ-protective actions, every MP patient should strive to take it at the suggested dose and frequency, which is 40mg, taken every 6 hours. In most cases, Olmesartan's palliative effects counteract the increase in immunopathology which occurs when its activation of the VDR starts to kill pathogens.

However, in some patients, Olmesartan's ability to turn on the innate immune response is so potent that the immunopathology rapidly becomes intolerable, even in the absence of taking antibiotics. In such cases, after consulting with their health practitioner, patients may temporarily lower their dose of Olmesartan -- if such an action gives them sustained symptomatic relief. However, they should continually strive to increase back to the suggested dose, when symptoms permit.

The reason for trying to achieve stability at the suggested dose is that if any vital organs become threatened, for example, heart, kidneys or lungs, the dose at which Olmesartan best protects those organs is even higher than nominal, as the half-life of Olmesartan's best anti-inflammatory activity is only about 4 hours. It is important for a physician to be able to prescribe the higher dose in an acute-care emergency.

Lowering the Olmesartan dose is a measure of last resort, and should only be contemplated after allowing time for hormonal rebalance, discontinuing supplements, abstaining from vitamin D, and fully avoiding outdoors exposure. Palliation with either Quercetin or Guaifenesin is preferable to reducing the Benicar dose.

In cases of hospitalization, and other critical care situations, the dosing of Olmesartan should not be reduced nor should it be discontinued, as organ failure has occurred subsequent to discontinuation of Olmesartan by hospital physicians.

Direct link to Emergency Room procedures: <http://AutoimmunityResearch.org/ER.pdf>

Although Olmesartan is a mild antihypertensive agent, even patients who have very low starting blood pressure (80/50) have tolerated Olmesartan well. While symptoms of dizziness, fatigue or lightheadedness are often associated with hypotension, during MP therapy they are usually the result of Th1 inflammation and they will resolve with time. Orthostatic hypotension is a common symptom of advanced chronic disease, and it often presents as immunopathology during recovery.

When initiating the Olmesartan blockade, the level of 1,25-D will be rapidly reduced. This often causes temporary neurological-type symptoms such as fatigue, lightheadedness, headache, photophobia, etc. These symptoms occur because the body has become accustomed to an abnormally high level of the steroid hormone 1,25-D, and many other hormones must shift (in reaction to the reduction in 1,25-D) to maintain homeostasis.

The level of 1,25-D is **not** an accurate predictor of a person's reaction to the Olmesartan hormonal adjustment or the severity of Immunopathology to be expected. A cautious person will always assume that symptoms may become severe at any time in the protocol and will follow all directions in this guideline carefully to prevent intolerable symptoms. Patients may ask for help on the study website, if needed, to manage severe symptoms.

Physicians should seek help from the Foundation to devise strategies to wean patients off other medications which may be interfering with the immune system, or whose effects may be exacerbated by Olmesartan's activation of the VDR.

See, for example, "Weaning from Corticosteroids":

<http://mpkb.mp-dev.com/doku.php/home:othertreatments:corticosteroids:weaningoffsteroids>

Intolerable Immunopathology can surprise a health care provider (or patient) who was previously unaware of the degree of systemic Th1 inflammatory involvement. Unexpected immunopathology can occur at any time, especially with each increase in antibiotic dose.

Some patients experience immunopathology when commencing Olmesartan alone, because Olmesartan restores proper functioning of the innate immune system, which will begin to kill the pathogenic bacteria. Occasionally these symptoms become intolerable. **The first option to reduce intolerable immunopathology is to take Olmesartan every 4 hours until the immunopathology subsides** (for months, if necessary). The second option (which may be used concurrently) is to dissolve half of an Olmesartan tablet (a dose of 20mg) under the tongue. **Additional Olmesartan should be kept on hand at all times.**

Patients experiencing intolerable immunopathology from Olmesartan alone, whose immunopathology is not controlled by more frequent dosing or sublingual bolus, should allow time for hormonal rebalance, discontinue supplements, abstain from vitamin D, protect their eyes (even indoors), and fully avoid outdoors exposure. An Olmesartan dosing regime of 20mg every 6 hours may be used as a temporary aid to help the patient's immune and hormonal systems to achieve stability. Palliation with either Quercetin or Guaifenesin should be attempted before deciding to temporarily lower the dose of Olmesartan.

The danger from using a lowered dose of Olmesartan is that its organ protective actions are most effective when the dosing cycle does not exceed 4 hours. This is because the pharmacodynamic half-life of organ protection is lower than the half-life of the VDR activation activity (and subsequent immune system activation). Thus, if the patient suffers an acute cardiac, pulmonary, or renal, crisis the full organ-protective actions will not be available from the lowered Olmesartan dosing regime. Consequently it is important to move to the suggested 40mg per 6hr dosing as soon as practical.

Patients with cardio-respiratory, liver, renal involvement or other serious health problems should be monitored very closely by their health care provider in order to properly manage Immunopathology and hormonal rebalancing.

It usually takes several weeks to stabilize symptoms on the Olmesartan blockade alone. This means that any additional symptoms have waned or resolved, and the patient feels able to tolerate an increase in symptoms from the expected Immunopathology when pulsed Minocycline is commenced. About 50% of patients experience no change or symptomatic relief from Olmesartan alone, about 25% take a few weeks to stabilize, but the most seriously ill may have to wait several months or more until their metabolites rebalance.

STEP FOUR

Continue to take Olmesartan (40mg every six hours).

Begin Minocycline. (If weaning from prednisone or cortef, wait two weeks after weaning is complete.)

- The recommended starting dose of Minocycline is 25mg taken every 48 hours (25mg every other day). **Do not use less.** Either generic or brand name is okay.
- Minocycline is only available in 50, 75 and 100mg capsules or tablets. Capsules may be opened to divide the contents into smaller portions to provide the needed dose. Use a pill splitter to cut tablets.
- **Do not substitute with doxycycline** because only Minocycline kills the bacteria that cause Th1 inflammation.

Be Alert for the Immunopathology

The MP medications are chosen for their effectiveness against the intra-cellular metagenomic microbiota. Bacterial die-off always elicits an inflammatory cytokine release from the cells they have parasitized. The result is Nitric Oxide (NO) release (eg manifested in BUN), and a temporary exacerbation of disease symptoms, a phenomenon called Immunopathology (IP).

Minocycline usually elicits the maximum immunopathology as its tissue concentration decays away to zero. Immunopathology typically begins 1–24 hrs after the Minocycline dose and usually dissipates 12–24 hrs before the next antibiotic dose. Many patients find the IP is strongest on the second day.

Anyone about to embark on the Marshall Protocol must understand that Immunopathology is unavoidable and will make them feel worse before they feel better. Patients should demonstrate a continued determination to recover their health, regardless of temporary symptom exacerbation.

Immunopathology may be an increase in current Th1 inflammation symptomatology, a return of previous symptoms or emergence of subclinical symptoms. Usually these symptoms are merely unpleasant, but they can be temporarily debilitating or serious.

The following is only a partial list of typical Immunopathology symptoms: fatigue, muscle weakness, rash, headache, photosensitivity, pain anywhere, numbness, nausea, diarrhea, constipation, ringing in the ears, toothache, sinus congestion, nasal stuffiness, fever/chills, flu-like body ache, cough, irritability, depression, sleep disturbances and 'brain-fog'.

Immunopathology is unique to each patient and their tissue involvement. When starting Olmesartan and Minocycline, it is not unusual to develop new, sometimes alarming, Immunopathology. For example, patients may experience sharp muscle or organ pains, wheezing, shortness of breath, and cardiac rhythm disturbances even in the absence of previous identification of problems in these areas.

Although rarely life-threatening, Immunopathology needs to be treated with respect. Carefully following the guidelines for Olmesartan and Minocycline should avert any serious problems.

Managing Severe Immunopathology when taking Olmesartan and Minocycline

Every physician and patient should be alert to the possibility of over-exuberant immunopathology and understand how to manage it. Patients who have had a cardiac workup, and have been warned of the possibility of cardiac involvement can be prepared with a full spectrum of management techniques and/or guided emergency instructions. **Primary amongst these tools is for the patient to have additional Olmesartan on hand**, if needed (see the discussion in step three)

Intolerable Immunopathology can surprise a health care provider (or patient) who was previously unaware of the extent of systemic Th1 inflammatory involvement. By provoking immunopathology,

Olmесartan and Minocycline are performing a therapeutic probe, providing information about unsuspected systemic inflammation. Intolerable immunopathology is difficult to predict, because even apparently innocuous factors, such as an increase in body temperature, can increase the intensity of the cytokine storm. Immunopathology can occur at any time, and with each increase in antibiotic dose.

Patients who exhibit severe cardiac involvement require special care. Please see the complementary document ***“Anticipating, Identifying and Treating Cardiac Symptoms While on the Marshall Protocol”*** at the study website.

http://autoimmunityresearch.org/cardiac_herx.pdf

- If Immunopathology becomes intolerable or involves significant cardiac or respiratory symptoms, **the dosage of Olmesartan should be increased to 40mg every four hours until symptoms subside** (see the discussion of Olmesartan dose in step three)
- **The patient should not take the next scheduled dose of Minocycline.**
- Patients are instructed to seek medical attention if they think they may be in trouble. .

A small fraction of patients exhibit increased immunopathology when dropping their minocycline dose to zero. In this case, restore the known stable dose for a 48 hour cycle, and then each subsequent 48hr dose should be reduced in 25mg steps to identify the lowest stable dosing of minocycline, which should then be maintained. Foundation staff should be consulted should any other problems arise.

The Immunopathology will continue until the unexpected bacterial load is reduced. The goal is always to achieve and maintain tolerable immunopathology throughout the several years of recovery.

Health care providers, who are unsure of the origin of new symptoms or their proper treatment, are encouraged to discuss the issues with staff by posting in the Health Professionals' forum at the study website.

STEP FIVE

Continue to take Olmesartan (40mg every six hours)

Incrementally increase Minocycline dose:

- Over several months, as the immunopathology at each dosing level gradually fades, increase the every-other-day Minocycline **slowly** in small, 25mg increments until the optimal level of 100mg every 48 hours is well tolerated.
- **Allow several weeks between increasing doses** to make sure the Immunopathology is not more than the patient wishes to tolerate. Once immunopathology has been induced, healing is occurring. There is no real benefit from hurrying any phase of the healing process.

Different bacteria and tissues can be targeted by different levels of Minocycline, so there is good reason to stay at each dosing level until Immunopathology is tolerable. **Patients may lower their Minocycline dose at any time if they need to lower immunopathology, for example, so they can attend a social event.**

Do not try to 'speed up' therapy by using a higher dose of Minocycline than the minimum needed to elicit tolerable Immunopathology. These are very slow-growing bacteria, and there is no need to hurry. **The dose of Minocycline that can be tolerated may change (both up and down) during the course of therapy.**

When the Olmesartan blockade and 100mg of Minocycline every other day no longer produce significant Immunopathology, the patient is ready to proceed to Phase Two. Some patients will be ready for Phase Two in a few months, some will take a few years. Study-site members may request the MP questionnaire to help determine if they are ready to proceed to Phase Two. Upon completion of the

questionnaire, the member will be admitted to the 'Phases Two and Three' forum at the study website. **Physician-members can identify those members who are in their care, and request they be given expedited access to the advanced forums.**

The following FAQs and tutorials may be helpful:

<p>Olmesartan (Olmesartan Medoxomil, Votum, ARB)</p>	<p><i>Why shouldn't we ramp up the dose of Olmesartan?</i> http://tinyurl.com/6fuks <i>The need for a Olmesartan blockade</i> http://tinyurl.com/lqtdn <i>How does Olmesartan work? Why is it superior to other ARBs?</i> http://tinyurl.com/7qmaf <i>I just started Olmesartan. Why do I feel worse?</i> http://tinyurl.com/6syqw <i>Does Olmesartan cause dizziness?</i> http://tinyurl.com/afxye <i>My blood pressure is already low. Can I take Olmesartan?</i> http://tinyurl.com/47m8y <i>How long should I stay on Olmesartan? Why don't I feel better? When should I start Minocycline?</i> http://tinyurl.com/5cozj <i>What is a therapeutic probe?</i> http://tinyurl.com/6amkk</p>
<p>Folates Food Light Lifestyle Vitamin D</p>	<p><i>D-Metabolites Tests</i> http://tinyurl.com/4bere <i>Vitamin-D Tutorial</i> http://tinyurl.com/5v5gu <i>The Important of Avoiding Vitamin D and supplemental Folic Acid</i> http://tinyurl.com/bmsq3 <i>Foods To Avoid</i> http://tinyurl.com/56ooc <i>The Effect of Sunlight/Daylight and Bright Lights</i> http://tinyurl.com/5kyef <i>The Effect of Light on the Brain (amygdala)</i> http://tinyurl.com/7427y <i>Protecting Your Eyes</i> http://tinyurl.com/qu48s</p>
<p>Hormones</p>	<p><i>Adrenal Function Tests</i> http://tinyurl.com/7ne5m <i>Hormonal-interaction Chart</i> http://autoimmunityresearch.org/hormones.pdf</p>
<p>Immunopathology (IP)</p>	<p><i>Immunopathology... what is it?</i> http://tinyurl.com/4feuk <i>What is a cardiac IP? When should I be concerned?</i> http://tinyurl.com/5grvv <i>My Immunopathology is too strong. What should I do?</i> http://tinyurl.com/45kju <i>How can I control my anxiety and depression?</i> http://tinyurl.com/9j8y3 <i>I have insomnia and fatigue. What should I do?</i> http://tinyurl.com/ctqyh</p>
<p>Sunscreens</p>	<p><i>Sunscreen overview:</i> http://tinyurl.com/ca7616</p>
<p>Minocycline</p>	<p><i>I'm allergic to an antibiotic on the protocol. Is there a substitute?</i> http://tinyurl.com/6ajax <i>Why do you NOT recommend tiny doses of Minocycline? How does low dose Minocycline work?</i> http://tinyurl.com/57cxp</p>
<p>Non-MP Medications Supplements</p>	<p><i>Medications to avoid when on the Marshall Protocol</i> http://tinyurl.com/66m2e <i>Is it safe to take anticoagulants while on the MP?</i> http://tinyurl.com/7rrmv <i>Why do I have to stop taking supplements?</i> http://tinyurl.com/4gpbl <i>Do I need to take a calcium supplement?</i> http://tinyurl.com/dcoxv</p>

document revision: initial release 6 Aug 2006, revised 10 April 09