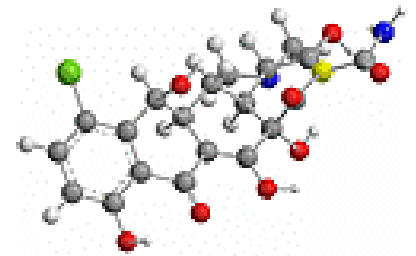


AUTOIMMUNITY RESEARCH FOUNDATION THE MARSHALL PROTOCOL – PHASE TWO



THE MARSHALL PROTOCOL – PHASE TWO

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2.0 Preface:

This revised document standardizes the second phase of the Marshall Protocol (MP) to simplify the process for the Healthcare Provider and patient.

It is essential for safety and efficacy that patients clearly understand all aspects of the MP and how to get help should they need it. These directions are spelled out in detail because many patients with Th1 inflammatory diseases also suffer from Th1-related cognitive difficulties. **Please give a printed copy of this document to your patients.**

Patients who are subjects in the MP clinical study cohort are posting a weekly progress report at the study site www.marshallprotocol.com and have access to 24/7 support there. Patients not in the clinical study should understand how to contact their Healthcare Provider when support is needed. Requesting a weekly report via email from your patient or a telephone contact from your clinic nurse will help ensure patient safety, provide efficient patient care and prevent emergency situations.

To facilitate the educational process for Healthcare Providers, we are pleased to offer at the study site, without charge, our extensive library of information about Th1 inflammation and treatment with the Marshall Protocol. Healthcare Providers (and their nursing staff) are encouraged to post general questions about MP management or specific questions about patient situations in the Health Professionals forum and join the scientific discussion in Dr. Marshall's Perspective.

The Healthcare Provider should determine readiness to proceed to phase two by assessing compliance with all aspects of the MP, especially lifestyle changes which involve diligently avoiding ingested Vitamin D and natural light or bright lights. A questionnaire is available in the Health Professionals Forum to facilitate this assessment.

2.0.1 Disclaimer:

This treatment guide is to be used by Healthcare Providers. The Autoimmunity Research Foundation assumes no responsibility for the use or misuse of this document.

2.0.2 Background:

The Marshalls' paper "Antibiotics in Sarcoidosis" [1] states that there are many different species of Cell Wall Deficient (CWD) bacteria which can contribute to Th1 inflammation. It has become clear that low dose, pulsed Minocycline (Mino) used in Phase One of the MP, while very effective, does not eliminate all the species of intra-phagocytic bacteria needed to effect a cure. After exhaustive research, the Marshalls have identified several other antibiotics which work by exerting a complimentary blockade of bacterial-protein synthesis. When these antibiotics are taken along with Mino (at low-dose, pulsed intervals), they are far more effective than if they were taken alone. **Benicar, taken 40mg every six hours both provides an inflammatory blockade and re-activates the VDR Nuclear Receptor.**

2.1 Azithromycin (brand names Zithromax and Sumamed):

The addition of a pulsed, low dose of azithromycin (Zithromax or Zith) makes a huge difference for those patients who are starting to plateau on the benefits available from Mino alone in Phase One. Zith by itself is not an effective treatment but it binds to the 50S Ribosomal Subunit in a manner which is symbiotic to the action of Mino on the 30S/50S interface.

Zith, combined with other MP antibiotics, is the 'big gun' among the MP antibiotics and must be used at some point during the MP.

Zith comes in 250mg or 500mg tablets, often in a package of 6 or 3, (Z-pack) but can be ordered in any number. 250 mg tablets will be easier to divide for the initial low doses.

Patients who are still experiencing significant immunopathology from 100mg of Mino every other day are not yet ready to proceed to Phase Two because the two-antibiotic combination is much stronger than Mino alone.

Patients with significant cardio-respiratory symptoms or tonic-clonic seizure activity should use the Modified Phase Two with Clindamycin (Clindy) before proceeding to Phase Two with Zith.

Clindamycin doesn't linger in the tissues like Zithromax so it is easier to control the immune system reactions (they will dissipate faster). This is important when serious reactions are a possibility. Modified Phase Two is described in detail later in this document.

Patients with significant psychological symptoms such as depression, anxiety, intrusive thoughts, obsessive-compulsive behavior should proceed to Phase Two (with Zithromax) because Clindamycin often exacerbates these symptoms to intolerable levels. For these patients, Clindamycin is usually tolerated better after Phase Two.

Using Clindy before Zith is a safety measure for those who might have serious IP symptoms. The need to use Clindy first postpones getting to the best combination of Mino, Zith and Clindy in Phase Three because **Phase Two must still be done after Modified Phase Two is completed.**

Patients who have had extreme difficulty tolerating Mino in Phase One despite compliance with avoiding lights may also need to progress to a Modified Phase Two before taking Zith.

2.2 Blood Tests:

At the beginning of Phase Two, Healthcare Providers should assess the level of 25-D. **It is vital for effective immune system function that this pre-hormone be at a low therapeutic level of 12ng/ml or less.** Patients whose levels of 25-D are still elevated should be encouraged to increase their efforts to avoid ingested forms of Vitamin D. It is not necessary to assess the level of 1,25-D at this point because it is altered by MP medications and is expected to fluctuate rapidly.

Healthcare Providers may want to check or recheck certain inflammatory markers such as triglycerides, creatinine, BUN, C-Reactive Protein (CRP) and alkaline phosphatase levels. The BUN, in particular, will rise because the intra-phagocytic microbiota give off nitric oxide as they are being killed. If lab results show levels of triglycerides, CRP or alkaline phosphatase, which were previously normal, have risen during Phase Two and/or Three, it is evidence of occult (hidden) Th1 inflammation, and the effectiveness of the MP.

Other lab tests which assess organ function (CMP with Mg, CBC with differential, TSH with free T3) should be monitored and may also change as the patient progresses on the MP. All lab work indicators of inflammation should eventually return to normal, as the patient's bacterial load is reduced.

2.3 Immunopathology:

Although rarely life-threatening, Immunopathology needs to be treated with respect. **Carefully following the schedule for introducing and increasing Zith should avert any serious problems.**

Because the combination of Mino and Zith is so effective at killing the intra-phagocytic microbiota, it can provoke a very strong immunopathology (IP). These reactions are difficult to predict because uncontrolled factors (e.g. an increase in body temperature can cause a sudden improvement in antibiotic tissue penetration, remodeled tissues can reveal new bacteria) with a resulting high bacterial kill and endotoxin release. It is typical of Zith to provoke the most powerful IP as its serum concentration is waning, on the third to sixth days of the ten-day cycle. But IP can occur at anytime during the dosing cycles and with each increase in a dosing level.

Immunopathology is unique to each patient and their tissue involvement. With the addition of Zith, it is not unusual to develop new, sometimes alarming, IP because this antibiotic combination eliminates organisms that were not susceptible to Mino alone. For example, patients may experience sharp muscle or organ pains, wheezing, shortness of breath and most disconcerting of all, cardiac rhythm disturbances even in the absence of previous identification of problems in these areas.

These reactions can surprise a Healthcare Provider (or patient) who was previously unaware of Th1 inflammatory involvement in these organs. By provoking IP, the antibiotics are actually performing a therapeutic probe, providing information about unsuspected systemic inflammation. To some extent, the degree of systemic involvement suggested by previous D-metabolites levels, other inflammatory blood markers, chest x-rays, severity of symptoms and length of illness will hint at the possibility of these serious IP reactions. But every patient should be alert to their possibility and understand how to manage them. Patients who have had a cardiac workup have the advantage of knowing of the possibility of coronary artery disease which might need emergency treatment.

2.3.1 Managing Severe Immunopathology:

Severe IP reactions may require quick action. Because Zith lingers in the tissues for 2-4 weeks, decreasing the dosage to manage an IP reaction (which works well with Mino or Clindy) is not an effective method with this long-acting antibiotic. If symptoms become intolerable or involve significant cardiac or respiratory symptoms, **the dosage of Benicar should be increased to 40mg every four hours around the clock until symptoms subside.** This is, in fact, the most effective treatment that has been identified.

The next dose of Zith should be postponed or reduced until symptoms are, once again, tolerable.

Adjusting Zith options:

- decrease the next dose
- take an early dose (the same or reduced) if symptoms peak on day 8-10
- delay the next dose (If Zith has accumulated in tissue after several cycles, however, symptoms may increase because Zith may be even more effective as the high tissue concentration wanes. In that case, reducing Zith and continuing with the 10-day cycle, if intolerable symptoms persist, may work better.)

Minocycline may also be adjusted to reduce IP.

Adjusting Mino options:

- reduce the dose first (lowest dose is 25mg)
 - extend the schedule to every third or fourth day
 - take an extra dose of 25mg (or 50mg if used to a higher dose)
 - discontinue until symptoms settle
 - take a low dose more often (25mg every 6 hours or 50mg every 12 hours or a daily dose of 25-50mg)
- Use past experience in Phase One to decide which option might work best now. When uncertain what to do when trying to reduce symptoms, it is best to first try reducing the Mino dose and/or delaying the next dose before trying an extra dose or frequent Mino dosing.

Other methods to manage the IP reaction, such as using quercetin, are discussed at the study site.

Do not increase antibiotic dose whenever you are requiring Benicar q4H to palliate symptoms

Healthcare Providers who are unsure of the origin of new symptoms, or their proper treatment, are encouraged to discuss the issues with Dr. Marshall either by phone or by posting in the Health Professionals Forum at the study site.

2.4 Other Medications:

ALL non-MP antibiotics are contraindicated for patients who are on the MP. Additional antibiotics could be dangerous because they may potentiate the MP antibiotics and provoke a severe IP reaction.

NOTE: Methotrexate (MTX) and Sulfasalazine are antimetabolite antibiotics with actions similar to Bactrim. Patients taking MTX or Sulfasalazine must discontinue these meds.

If a non-MP antibiotic is needed for an acute infection, all MP antibiotics should be discontinued.

Where possible, the fluoroquinolones are recommended as least likely to target CWD bacteria or to cause a IP reaction. If a fluoroquinolone is used, Benicar may be continued. Healthcare Providers may contact the study site or Dr. Marshall for more details.

2.5 IMPORTANT INFORMATION FOR PATIENTS (Please Read):

Although rarely life-threatening, the IP reaction needs to be treated with respect.

If you develop intolerable symptoms or cardiopulmonary symptoms such as heart rhythm irregularities or severe difficulty breathing or severe throat constriction or severe abdominal pain:

- Increase Benicar to 40mg every three hours. When in a 'crisis', take an extra 20mg of Benicar sublingually **with** each every three hour oral Benicar dose. This is especially important if you have GI tract inflammation. Continue until symptoms are tolerable (Your Healthcare Provider understands why this is necessary to ensure complete blockade of inflammatory cytokines).
- Contact your Healthcare Provider immediately (S/he may call Dr. Marshall if necessary).

-Seek emergency medical attention if you have any doubts about the severity of your symptoms.

-If you are a member of the clinical study cohort, you may post a message in the Urgent Forum to obtain additional information on decreasing a severe IP reaction.

The next dose of Zith should be postponed or reduced until symptoms are, once again, tolerable.

Adjusting Zith options:

-decrease the next dose

-take an early dose (the same or reduced) if symptoms peak on day 8-10

-delay the next dose (If Zith has accumulated in tissues after several cycles, however, symptoms may increase because Zith may be even more effective as the higher tissue concentration wanes. **In that case, reducing Zith, if intolerable symptoms persist, may work better.**

Minocycline may also be adjusted to reduce IP.

Adjusting Mino options:

-reduce the dose first (lowest dose is 25mg)

-extend the schedule to every third or fourth day

-take an extra dose of 25mg (or 50mg if used to a higher dose)

-discontinue until symptoms settle

-take a low dose more often (25mg every 6 hours or 50mg every 12 hours or a daily dose of 25-50mg)

Use past experience in Phase One to decide which option might work best now. When uncertain what to do when trying to reduce symptoms, it is best to first try reducing the Mino dose and/or delaying the next dose before trying an extra dose or frequent Mino dosing.

-Consult your Healthcare Provider if you are worried about any symptoms.

Your reactions to Zith and your progress will vary. **Do not expect each cycle to be a repeat of the previous cycle.** If IP reactions become a problem at any time, reduce the Zith and/or Mino to a lower dose. The goal of Phase Two is to kill more species of bacteria than Phase One. However, it is important to manage the antibiotic dosage using incremental dosing levels which control the IP and avoid uncomfortable or even dangerous reactions. **There is no advantage to proceeding too quickly.**

2.6 Zithromax dosing schedule for Phase 2:

Patients taking Zith will have to live with and manage its IP consequences for some days or even weeks. Therefore, we suggest all patients proceed very slowly and cautiously with the addition of Zith to minimize the possibility of severe IP reactions. Dr. Marshall and/or the Board Staff at the study site are available to offer important insights regarding MP management to Healthcare Providers.

Healthcare Providers should remember the patient's perception of their IP reactions and what is 'intolerable' is an integral part of guiding the Zith dosing schedule. Adjustments should be made **as indicated in the schedule** based on the IP reactions that the patient decides s/he is willing to tolerate. Unless intolerable symptoms are sudden and serious, it is best not to make more than one dosing or med change at a time so it will be easier to assess if this change was effective.

A foundation inflammatory blockade of Benicar at 40mg every 6 hours, in addition to light and Vitamin D restrictions, is continued throughout Phases Two and Three.

Follow this recommended schedule carefully.

First level of dosing Zith in 10-day cycles:

Reduce Mino to 25mg. Wait to ramp Mino until the second cycle when you have had a chance to assess the effect of this new combo.

You may start with less than 31.25mg of Zith if you feel the need to be extra cautious.

Day 1-Benicar + Mino + **31mg of Zith** (This is 1/8 of a 250mg tablet. Crush or use a pill cutter to divide it into eighths)

Day 2-Benicar only

Day 3-Benicar + Mino (symptoms may peak from days 3 to 6)

Day 4-Benicar only

Day 5-Benicar + Mino

Day 6-Benicar only

Day 7-Benicar + Mino

Day 8-Benicar only

Day 9-Benicar + Mino

Day 10-Benicar only

If your IP reaction was intolerable during this first cycle of 31mg Zith - do not take another Zith on day 11, just continue Benicar and 25mg Mino every other day. Then, wait until symptoms are tolerable again before taking another 31.25mg (or less) of Zith. (Remember Zith stays in your tissues for 2-4 weeks.)

Ramp up Mino by 25mg increments **starting with the second cycle** only if symptoms are tolerable.

Do not increase Mino on days when Zith usually peaks (days 3-6 and 9).

Stay at the same dose of Mino until symptoms are tolerable.

The level (dose) of Zith may not change on day 1 of many 10-day cycles.

Do not increase this initial level of Zith until you have slowly ramped Mino to 100mg and symptoms have been tolerable **for an entire 10-day cycle**.

Repeat this 31mg 10-day cycle before increasing the dose of Zith, even if symptoms were tolerable.

Second level of Zith dosing in 10-day cycles:

Reduce Mino to 25mg again.

Day 1-Benicar + Mino + **62mg of Zith** (1/4 of 250mg tablet)

Day 2-Benicar only

Day 3-Benicar + Mino (symptoms may peak from days 3 to 6.)

Day 4-Benicar only

Day 5-Benicar + Mino

Day 6-Benicar only

Day 7-Benicar + Mino

Day 8-Benicar only

Day 9-Benicar + Mino

Day 10-Benicar only

If your IP reaction was intolerable during this cycle of 62mg Zith - Follow previous instructions to reduce IP symptoms.

Ramp up Mino by 25mg increments **during each cycle** only if symptoms are tolerable.

Do not increase Mino on days when Zith usually peaks (days 3-6 and 9).

Stay at the same dose of Mino until symptoms are tolerable.

The level (dose) of Zith may not change on day 1 of many 10-day cycles.

Continue 62mg of Zith in 10-day cycles until you have slowly ramped Mino to 100mg and symptoms have been tolerable **for an entire 10-day cycle.**

Third level of Zith dosing in 10-day cycles:

Reduce Mino to 25mg again.

Day 1-Benicar + Mino + **93mg of Zith** (3/8 of a 250mg tablet)

Day 2-Benicar only

Day 3-Benicar + Mino (symptoms may peak from days 3 to 6.)

Day 4-Benicar only

Day 5-Benicar + Mino

Day 6-Benicar only

Day 7-Benicar + Mino

Day 8-Benicar only

Day 9-Benicar + Mino

Day 10-Benicar only

If your Immunopathology was intolerable during this cycle of 93mg Zith - Follow previous instructions to reduce IP symptoms.

Ramp up Mino by 25mg increments **during each cycle** only if symptoms are tolerable.

Do not increase Mino on days when Zith usually peaks (days 3-6 and 9).

Stay at the same dose of Mino until symptoms are tolerable.

The level (dose) of Zith may not change on day 1 of many 10-day cycles.

Continue 93mg of Zith in 10-day cycles until you have slowly ramped Mino to 100mg and symptoms have been tolerable **for an entire 10-day cycle.**

Fourth Level of dosing in 10-day cycles:

Reduce Mino to 25mg again.

Day 1-Benicar + Mino + **125mg of Zith** (1/2 of a 250mg tablet)

Day 2-Benicar only

Day 3-Benicar + Mino (symptoms may peak from days 3 to 6.)

Day 4-Benicar only

Day 5-Benicar + Mino

Day 6-Benicar only

Day 7-Benicar + Mino

Day 8-Benicar only

Day 9-Benicar + Mino

Day 10--Benicar only

If your Immunopathology during this cycle of 125mg Zith was intolerable - Follow previous instructions to reduce IP symptoms.

Ramp up Mino by 25mg increments **during each cycle** only if symptoms are tolerable.

Do not increase Mino on days when Zith usually peaks (days 3-6 and 9).

Stay at the same dose of Mino until symptoms are tolerable.

The level (dose) of Zith may not change on day 1 of many 10-day cycles.

Continue 125mg of Zith in 10-day cycles until you have slowly ramped Mino to 100mg and symptoms have been tolerable **for an entire 10-day cycle.**

Then you should progress to Phase Three.

Note: Do not take more than 125mg of Zith. This exceeds the minimum inhibitory concentration (MIC) and provides the necessary antibiotic action without threat of side effects during extended use.

2.7 Modified Phase 2:

Patients with a history of significant cardiac symptoms, severe respiratory symptoms or tonic-clonic seizures are advised to discuss with their Healthcare Provider the option of progressing from Phase One to a Modified Phase Two.

Modified Phase Two adds incremental levels of generic clindamycin (brand names include Cleocin and Dalacin) with the every-other-day minocycline instead of the Zithromax (Zith) described in Phase Two. Clindamycin doesn't linger in the tissues so it is easier to control the IP reactions in a short period of time. This is important when serious or intolerable reactions are a possibility with Zith.

Note: Clindamycin (Clindy) is particularly effective at eliminating CWD bacteria located in nerve tissue. Consequently, IP reactions often involve exacerbation of Th1-related psychological symptoms. Therefore, patients with anxiety, depression, OCD, etc. who must use Clindy before Zith should ramp Clindy cautiously, as symptoms allow, and be monitored closely.

Please read these Instructions very carefully. Patients should contact their Healthcare Provider if they have **ANY** Questions.

Healthcare providers can order 150mg capsules of clindamycin (the generic form is fine).

Reduce the dose of Mino to 25mg every other day when you add Clindy.

Take the Clindy dose every other day at the same time as your Mino dose. Only the dose level is varied in the options below, not the timing.

As symptoms allow, ramp Clindy incrementally to:

37.5mg (1/4 capsule)

75mg (1/2 capsule)

112.5mg (3/4 capsule)

150mg (full capsule) This is the maximum dose.

It's okay to start with and/or increase Clindy in smaller increments or very tiny doses.

Mino is ramped in 25mg increments to a maximum dose of 100mg.

There is no one preferred or recommended ramping option. Mino and Clindy may be increased in any order but **ramp one at a time**. After you make an adjustment and assess your response, you may find that you prefer to use one pattern of ramping.

Stay at each dose level for a minimum of 3-4 doses with tolerable symptoms **at all times** before increasing unless experience tells you that an increase would dampen intolerable symptoms.

Note: Clindy may provoke an IP reaction immediately or it may take a few weeks for it to provoke a reaction. Be patient and be alert for an increase in psychological symptoms such as depression, insomnia, anxiety, moodiness, obsessive-compulsive behavior, irritability and anger.

If symptoms become intolerable, first increase Benicar to every four hours around the clock until symptoms are tolerable.

If you have trouble with neuro symptoms, you can continue Mino as usual and adjust Clindy using these options:

-reduce the dose....it's okay to take a very tiny dose of Clindy.

-dose Clindy every third day instead of every other day.

-skip a dose and take Clindy every four days only with the 2nd every other day dose of Mino.

-extend Clindy to once per week.

You may also follow previous instructions regarding adjusting Mino to reduce IP symptoms.

The maximum Modified Phase Two dose is 100mg Mino and 150mg of Clindy taken together every other day.

Note:

The use of other two-antibiotic combinations (Minocycline or Demeclocycline and Bactrim) as another form of Modified Phase Two may be advantageous for those few patients who have had a difficult time tolerating the Immunopathology from Mino and/or Clindy. These combinations may be used to further reduce the bacterial load before using the most powerful two-antibiotic combo of Mino and Zith in Phase Two.

2.8 Proceeding to Phase 2 after Modified Phase 2:

You must progress through phase two with Zith before you proceed to Phase Three.

To make the transition, **discontinue Clindy** (and Deme or Bactrim if you were taking either) two days before you plan to begin Zith (you should take the usual 100mg Mino). Otherwise, you may experience a powerful immune response from a 3-antibiotic combo. Two days later, **reduce mino to 25mg** and take it with your first dose of Zith. Please refer to the previous detailed instructions in this document regarding Phase Two.

2.9 Proceeding to the next Step – Phase 3:

When you can tolerate the IP from 125mg Zith every 10 days with 100mg Mino every other day, it is recommended you move to Phase Three and add Clindamycin (Clindy). It is advantageous to progress to the Mino + Zith + Clindy combination as soon as possible because this is the most effective combination and their symbiotic relationship reduces the chance of CWD bacterial resistance with long-term use.

Dr Marshall states: "**Mino+Zith+Clindy is the optimal antibiotic combination.** Everyone should be taking it as soon as they are able to handle the Immunopathology. Mino blocks the 30S Ribosomal subunit, Clindy blocks the 50S subunit at the peptidyl transferase center and Zith blocks the protein exit route of the 50S. All three work symbiotically."

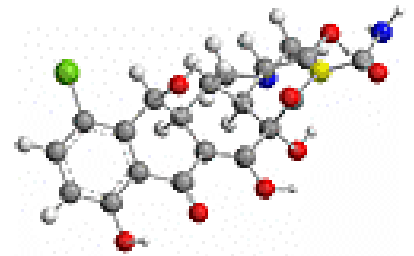
***Note:** If you have been on the Marshall Protocol one year or more, have been diligently avoiding all light exposure, and are not yet taking a three-antibiotic combo, it is suggested that you consult your Healthcare Provider about progressing to Phase Three. Dr. Marshall has provided evidence a lower dose of three antibiotics will be more effective than a higher dose of only two.*

Reference:

[1] Marshall TG, Marshall FE Antibiotics in Sarcoidosis - Reflections on the First Year. JOIMR 2003;1(3)2 Available from <http://www.joimr.org/phorum/read.php?f=2&i=38&t=38>

AUTOIMMUNITY RESEARCH FOUNDATION

THE MARSHALL PROTOCOL – PHASE THREE



3.0 Preface:

This revised document standardizes the third phase of the Marshall Protocol (MP) to simplify the process for the Healthcare Provider and patient

It is essential for safety and efficacy that patients clearly understand all aspects of the MP and how to get help should they need it. These directions are spelled out in detail because many patients with Th1 inflammatory diseases also suffer from Th1-related cognitive difficulties. **Please give a printed copy of this document to your patients.**

Patients who are subjects in the MP clinical study cohort are posting a weekly progress report at the study site www.marshallprotocol.com and have access to 24/7 support there. Patients not in the clinical study should understand how to contact their Healthcare Provider when support is needed. A weekly report via email or telephone contact from your clinic nurse will help ensure patient safety, provide efficient patient care and prevent emergency situations.

To facilitate the educational process for Healthcare Providers, we are pleased to offer at the study site, without charge, our extensive library of information about Th1 inflammation and treatment with the Marshall Protocol. Healthcare Providers (and their nursing staff) are encouraged to post general questions about MP management or specific questions about patient situations in the Health Professionals forum and join the scientific discussion in Dr. Marshall's Perspective.

3.0.1 Disclaimer:

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3.1 Phase Three:

The third phase in the standard MP progression is adding Clindamycin (Clindy) to Mino and Zith. Clindamycin brand names include Dalacin and Cleocin.

Reduce Zith to 31.25mg and Mino to 25mg when you add the initial dose of Clindamycin. The starting dose of Clindy is 1/4 or 1/8 (or less) of 150mg capsule.

Clindy and Mino are taken together on day 1 of the 10 day Zith cycle and then every other day or every 3 days.

Ramp only one antibiotic at a time and remember the new antibiotic (Clindy) may take a few days to kick in.

Be sure to assess the immune response as being tolerable after each increase before making another increase.

Keep in mind that Mino and Clindy can be adjusted more quickly than Zith, so it is easier to control the immune response with them.

3.2 Dosage Ramping Schedules:

Dosing option one (ramp Clindy first):

Keep Mino and Zith at starting levels until Clindy is ramped to the maximum dose of 150mg every other day.

- Take 31mg Zith once every ten days.
- Take 25mg Mino and Clindy every other day at the same time.
- Start with just 1/4 of the 150 mg Clindy capsule (37.5mg). Take it **every other day** with the Mino.
- As symptoms allow, ramp Clindy by 1/4 capsule increments every week or two until the maximum dose of 150mg every other day is reached.
- Then, as symptoms allow, ramp the every-other-day Mino up by 25mg increments until you reach 100mg every other day.
- Then, as symptoms allow, increase Zith levels by 31mg increments following the 10 day schedule for Zith dosing until you are once again taking 100mg Mino every other day and 125mg Zith every 10 days.

Dosing option two: (ramp one antibiotic at a time)

- Keep Clindy at the starting level of 1/4 capsule taken every other day at the same time as Mino.
- Keep Zith at the starting level of 31mg every 10 days.
- As symptoms allow, ramp the every-other-day Mino up by 25mg increments until you reach 100mg every other day.
- Then, as symptoms allow, increase Zith levels by 31mg increments (following the 10 day schedule for Zith dosing) every 2 cycles until you are once again taking 125mg Zith every 10 days.
- Then, as symptoms allow, ramp Clindy by 1/4 capsule increments every week or two until you reach a maximum dose of 150mg.

Dosing option three: (ramp all 3 antibiotics in an alternating or zig zag pattern):

- Use the starting doses of 31mg Zith every 10 days plus 25mg Mino every other day plus 1/4 150mg capsule of Clindy every other day.
- As symptoms allow, ramp each antibiotic, described above, in an alternating pattern until you are taking the maximum dose of all three.

You may:

- ramp Mino to 100mg first
- ramp Clindy to 150mg first
- ramp Zith to 125mg first
- alternate ramping two or all three antibiotics to maximum doses

When ramping the Zith we recommend decreasing your Mino and Clindy doses till you assess the immune response, and then increase them as is tolerable.

The maximum end doses of this combination are:

- 125 mg of Zithromax
- 150mg of Clindamycin
- 100mg Minocycline

You may continue the optimal target combination of 100mg Mino every other day plus 150mg Clindy every other day plus 125mg Zith every 10 days for as long as it provokes a IP reaction. This may last for many months, sometimes for several years.

You may also extend the Mino and/or Clindy schedule to every 3 days in an effort to provoke or better tolerate a IP reaction. Do not take Zith more often than every 10 days or more than 125mg.

125mg of Zith is the maximum dose of Zith when taking three antibiotics. Do not take more than 125mg of Zithromax. This dose exceeds the minimum inhibitory concentration (MIC) and provides the necessary antibiotic action without threat of side effects during extended use.

3.3 Other Three Antibiotic Combinations:

Because there are so many species of intracellular bacteria that cause Th1 inflammation, we recommend a variety of antibiotic combinations to finally eliminate all of them. After you have exhausted the immunopathology with Mino/Zith/Clindy, every couple of months or so we recommend the use of further antibiotic combinations until you no longer have an IP response.

The antibiotic combinations should include every-other-day Minocycline because Mino is the primary, synergistic antibiotic.

Reduce all antibiotics to starting doses when you try a new combination and ramp up one at a time as symptoms allow.

Zithromax is still taken in 10-day cycles on day one; never taken more often than every 10 days or more than 125mg when in a three-antibiotic combination.

It is important to choose doses and combinations at any point in time which result in immunopathology symptoms that are manageable. Eventually you will have to have used all of the antibiotics combinations until you no longer react to any. It will take many years to get to that stage, and you will have been 'cured' years before you reach it.

3.4 Other Antibiotics:

Bactrim comes in DS (Double Strength 800/160mg) or RS (Regular Strength 400/80mg). Bactrim is the brand name. It is also known as Septra, Sulfatrim, Cotrim, Novo-Trimel, Nu-Cotrimox, Resprim, Roubac and Septrin. The generic name is co-trimoxazole. Regular strength is a combination of 400mg of sulfamethoxazole and 80mg of trimethoprim. Either generic or brand name is appropriate to use.

Many patients with Th1 inflammation have been told that they are allergic to sulfa preparations. The 'allergic' reaction experienced in the past was most likely an IP reaction. These patients should begin with 1/4 tablet (or less) of REGULAR STRENGTH Bactrim and ramp up by 1/4 increments every 2 weeks (or as symptoms allow) to a full tablet and then progress to Bactrim DS. Cutaneous reactions (pruritus and rash) are common and may be treated palliatively.

CBC with differential will help identify those very few pts who may develop a rapid drop in RBC, which would require lowering of the Bactrim dosage.

Patients who have not had a previous reaction to a sulfa drug may begin with 1/4 tablet of a Double Strength tablet and ramp up by 1/4 tablet increments every 2 weeks (or as symptoms allow) to a maximum dose of a full DS tablet.

Bactrim is taken every other day with the Mino dose.

Declomycin (demeclocycline) is a rarely used form of tetracycline, very similar (chemically) to Minocycline but it seems to target different CWD bacteria. It comes in 150mg tablets (the maximum dose recommended). It is expensive in the US, but has proven, for some, to provoke stronger reactions than Mino. 150mg of Demeclocycline (Deme) can be used in any of the various three-antibiotic combinations. It is best used with Zith or Clindy to increase the spectrum of targeted bacteria.

Demeclocycline is taken at the same time as every-other-day antibiotics.

Possible three-antibiotic combinations:

Mino + Zith + Clindy

Deme + Zith + Clindy

Mino + Zith + Bactrim

Deme + Zith + Bactrim

Mino + Clindy + Bactrim

Deme + Clindy + Bactrim

Deme + Zith + Mino

Deme + Clindy + Mino

Deme + Bactrim + Mino

Continue the Benicar blockade at 40mg every 6 hours.

- Vary the three-antibiotic combinations.
- Do not take more than three simultaneous antibiotics.
- Try all possible combinations more than once to ensure a total intracellular bacterial elimination.
- Continue a three-antibiotic combination until no significant reaction is provoked.
- You may extend Mino, Deme, Bactrim or Clindy doses to every 3 days in an effort to provoke a reaction.

The two-antibiotic variation:

When the 3-antibiotic combination no longer provokes an IP reaction, you may discontinue 1 of the 3 antibiotics and ramp up to 250mg of Zith using the standard 10-day cycles to see if that dose provokes IP reactions. Do not take more than 250mg of Zith. Do not take 3 antibiotics with this dose (250mg) of Zith.

3.5 Formal Marshall Protocol Endpoints:

Full recovery is indicated by:

- resolution of symptoms
- return of function
- absence of immune system reaction to MP antibiotics
- return of ACE, CRP, triglycerides, ALP to low end of normal
- Increase in % lymphocytes, back into the normal range
- 1,25-D at 25-35pg/ml measured over a 6 month interval
- signs of inflammation resolution on CT and MRI imaging

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