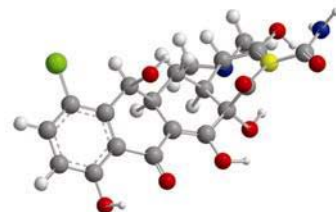


Anticipating, Identifying and Treating Cardiac Herxheimer Symptoms in Patients using the 'Marshall Protocol'



Anticipating cardiac symptoms

The Th1 immune system response to intra-phagocytic bacteria results in low-grade, often subclinical inflammation and chronic disease. Its effects can be seen in any part of the body, including any area of the heart.

Studies have shown that people with immune diseases, like RA and lupus, have an increased risk of heart attack. Recent research has revealed the role of inflammation in the development and progression of coronary artery disease. Several studies, suggest inflammation causes a sequence of actions in the coronary artery (*i.e.* plaque rupture, thrombus formation and embolization) to trigger myocardial infarction (MI).

Treating Th1 inflammation with the Marshall Protocol (MP) unavoidably results in repeated Jarisch-Herxheimer (Herx) reactions which temporarily increase existing inflammation [1]. While a severe cardiac Herx reaction is rare, it has the potential to be life-threatening. Therefore, we caution health care providers to be on the alert for cardiac symptoms in all their patients.

Identifying cardiac inflammation

Th1 inflammation in the heart is subclinical long before the damage it causes is detected by tests. Gross evidence of cardiac inflammation is only picked up in its advanced stages by echocardiogram or magnetic resonance imaging (MRI). A biopsy of the heart to obtain a definitive diagnosis is dangerous, often imprecise and unnecessary.

The secosteroid 1,25-dihydroxyvitamin-D (1,25-D) is an excellent marker of Th1 inflammation. A level above 50pg/ml (hypervitaminosis-D) suggests the presence of inflammation in a major body organ such as the heart. Consider further testing if 1,25-D is elevated, the patient has a history of heart disease or has cardiac symptoms.

A cardiac workup will provide valuable information to the health care provider about the presence or absence of cardiovascular disease. This knowledge will help assess any cardiac symptoms that may emerge while on the MP. A diagnosis of probable cardiac inflammation is based on tests and symptoms, including, but not limited to: chest pain, mitral valve prolapse, and all types of arrhythmia.

A baseline electrocardiogram (ECG) or exercise stress test is helpful to diagnose future arrhythmias and ambulatory monitoring may be necessary for transient symptoms of arrhythmia. Positive emission tomography or computed tomography and measurement of biomarkers such as creatine kinase, lactic de-hydrogenase, serum aspartate aminotransferase, and troponin may be considered for those with questionable chest pain. The possibility of ischemia or MI can then be estimated on the basis of the magnitude of biomarker elevation, new ECG abnormalities, hemodynamic instability, quality and intensity of chest pain or other symptoms. Nimata, *et al* describe how hypervitaminosis-D can mimic an MI [2].

Other inflammatory markers are also used to detect risk of heart disease. Elevated c-reactive protein has been related to increased risk for MI, re-stenosis of coronary arteries after angioplasty, stroke, and peripheral vascular disease. Increased levels of myeloperoxidase and interleukin 6 have been associated with an increased risk of death in patients with heart disease.

Brain natriuretic peptide and N-terminal prohormone brain natriuretic peptide B-NP are cardiac markers which can diagnose and assess the severity of heart failure. MRI, echocardiogram, nuclear imaging, cardiac catheterization or transesophageal echocardiogram can reveal other heart

abnormalities and may be necessary for symptomatic patients at high risk for a cardiac event.

Since cardiac Th1 inflammation is extremely difficult to diagnose definitively, the presence of cardiac symptoms or elevated inflammatory markers in someone with a Th1 inflammatory disease should be considered a strong indicator there is some degree of cardiac involvement. It can be assumed any patient with a Th1 inflammatory disease may have undiagnosed cardiac inflammation.

Helping patients identify serious cardiac symptoms

Herx reactions can present as chest pain or pressure, left arm pain, jaw pain, increased dyspnea, sweating and nausea. Chest pain and pressure can be caused by other structures within the chest wall besides the heart. However, because chest pain and pressure may be due to coronary insufficiency, **these symptoms should always be considered an emergency due to possible MI unless coronary artery disease has been ruled out recently.**

Instruct patients to seek medical attention immediately if they have any concerns about their cardiac symptoms. Encourage patients to follow their instincts and call for emergency help if they think they need it. Caution them to ask someone to stay with them or drive them to the clinic if the situation is not an emergency.

Patients may ask for help managing their Herx reaction on the study website, www.marshallprotocol.com. If a symptom is serious, after calling their health care provider, they may post for suggestions in the URGENT PROBLEMS ONLY forum which is monitored 24/7 by nurse moderators.

Cardiac arrhythmias are not uncommon with Th1 inflammation. Instruct patients to report:

Any rhythm change that is:

- very slow (below 50 beats per minute)
- very rapid (above 160 beats per minute)
- extra beats that are very frequent (more than 10 per minute)
- unusually long intervals between beats (more than 3 seconds).

Patients should also report symptoms suggestive of congestive heart failure:

- a change in exercise tolerance
- increased dyspnea
- sudden weight gain or edema

Patients who are photosensitive (sensitive to sun exposure on their skin and/or in their eyes), may have increased cardiac symptoms during or after exposure. The first treatment action should be to limit sun exposure and assess symptom resolution. If symptoms persist, follow the guideline for treating a Herx reaction.

Treating a cardiac Herx reaction

Cardiac arrhythmias related to the Herx reaction do not respond well to the usual anti-arrhythmic medications. The best way to treat these cardiac symptoms, is by **increasing Benicar 40mg to every four hours** to provide a strong anti-inflammatory blockade which reduces inflammation.

This more frequent dose may be continued until symptoms resolve or are tolerable. There are no reports of adverse reactions to this increased dose. A recent Sankyo study (although small), confirms the safety profile of Benicar noted in the MP Phase II study cohort. It shows single-dose pharmacokinetic linearity of Benicar to 160mg, and another to 320mg, without adverse effect [3]. If in doubt about the wisdom of the increased Benicar blockade, consider the risk of cardiac symptoms versus the apparently minor risk of extended q4h Benicar dosing.

In addition to increasing Benicar dosing frequency, **the next dose of antibiotic/s should be omitted.** Zithromax lingers in the tissues for several weeks and these patients may need to manage their Herx

symptoms for some time. For this reason, patients with a history of cardiac symptoms are advised to add Clindamycin to Minocycline before using Zithromax. With Clindamycin, Herx reactions are easier to manage and Clindamycin will reduce the bacterial load before using the more challenging Zithromax.

NOTE: If increasing Benicar and stopping antibiotics does not reduce the Herx reaction, **patients may also alter their antibiotic dose and schedule in various ways to dampen the Herx reaction** [4].

A Herx reaction sometimes takes the form of anxiety, which may magnify symptoms. Patients who are anxious may find the introduction of an anxiolytic reduces the severity of cardiac symptoms [5].

Note: The antibiotic dose should not be increased until significant cardiac Herx symptoms have resolved at the current level of antibiotic.

Treating the runaway Herx reaction

If all medication adjustments [4] have been tried and the patient is still Herxing intolerably, **you may wish to consider dexamethasone as a temporary 'last resort'**.

To use dexamethasone:

1. Continue Benicar at 40mg every six hours and the current antibiotics/dose schedule.
2. Begin 250micrograms of dexamethasone every 6 hours. This may be increased to 500micrograms every 6 hours if needed.
3. Dr. Marshall has computed the molecular genomic profile of this corticosteroid on the nuclear receptors [6]. Dexamethasone has a more benign profile than prednisone, yet it does suppress peroxisome proliferator-activated receptors (PPARs) and vitamin D receptors (VDRs), and thus the Th1 response, well enough. The few patients who have needed this intervention have reported that 250mcg of dexamethasone every 6 hours has brought their Herx reaction under control.
4. When Dexamethasone has controlled the runaway Herx reaction, gradually reduce the dose. This should be a short-term process but the *Weaning From Steroids* guideline, may be helpful [7].
5. The goal of this intervention is to gain control of Herx symptoms quickly, wean from the Dexamethasone and then alter the MP antibiotics one at a time to achieve bacterial killing with tolerable Herxing as per the MP guidelines.

To discuss scientific issues you may contact Dr. Marshall at Trevor.m@yarcip.com or 805-492-3693.

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