You asked…

What role does doxycycline play in the management of heartworm disease?

The exact role of doxycycline in the management of heartworm disease (HWD) is not well established. However, virtually all experts in the field would agree that doxycycline has a role in therapy and most U.S. veterinarians incorporate it into their management of HWD (Figure 1).

Several important questions regarding doxycycline remain unanswered, including:

• What is the optimum concomitant therapy (ie, most data to date have been generated using concomitant administration of ivermectin)?
• What is the exact dosage, time-point for initiation, and duration of therapy?
• What are the risk and cost to benefit ratios?
• In which specific disease stage(s) is doxycycline useful?

Doxycycline versus Wolbachia

The benefits of doxycycline result from its ability to remove or reduce the burden of Wolbachia, a rickettsial organism that exists in a symbiotic relationship with heartworms (and other filarids), occupying the reproductive tract and lateral chords of the host parasite (Figure 2).
Wolbachia are necessary for the parasite (in this case, Dirofilaria immitis) to develop, thrive, reproduce, and maintain infectivity.

Doxycycline has been used to (presumably) rid the parasite of Wolbachia organisms; therefore, D immitis organisms do not thrive, may deteriorate and die, and have reduced reproductive potential, which helps manage HWD in infected dogs and reduces potential for infection in other dogs.

Potential and realized benefits derived from anti-Wolbachia therapy include:

1. Reduced Ability of Parasite to Reproduce
   - It has been shown that the Wolbachia organism is suppressed (killed) by doxycycline and the resulting, negative effects on the heartworm reproductive system renders the parasite infertile or less fertile (temporarily?), with reduced microfilarial numbers.1,2,3

2. Reduced Infectivity
   - In doxycycline-treated dogs, even if microfilariae are produced and ingested in a mosquito’s blood meal, the resultant L3 are incapable of producing infection, reducing the spread of HWD.1,2,3

3. Potentiate Adulticidal Therapy and/or Enhancement of Slow- or Soft-kill Efficacy
   - Most agree that Wolbachia is an obligatory symbiont for D immitis, which gives hope that Wolbachia eradication with antibiotics would result in the nematode’s demise. Unfortunately, prolonged doxycycline therapy does not kill heartworms because they are not sufficiently bound to their bacterial symbionts.4
   - Nevertheless, 2 studies5,6 have demonstrated that doxycycline shortens the time until worm death when administered chronically with ivermectin/pyrantel at preventive dosages, but with a decreased dosing interval.5,6

Study 1: Using surgically transplanted worms, it was shown that a combination of:

- Weekly ivermectin (at the monthly preventive dosage of 6 mcg/kg PO) and
- Daily doxycycline (10 mg/kg PO Q 24 H for 24 weeks of a 36-week study) reduced heartworm burden by 78% after 9 months of therapy as compared to control dogs.5

Study 2: Using echocardiography, this study evaluated the effect of:

- Daily doxycycline (10 mg/kg PO Q 24 H for 30 days) and
- Ivermectin/pyrantel (6–14 mcg/kg PO every 15 days for 180 days; then monthly) on microfilaraemia, heartworm antigenemia, and parasite load. In naturally-infected dogs from an endemic region of Italy, all dogs became negative for circulating microfilariae by day 90 and 73% became antigen negative by day 300.7

The results of these studies suggest that the combination of doxycycline and ivermectin is (slowly) adulticidal in dogs with D immitis, which indicates that doxycycline enhances therapy for the soft- or slow-kill method.

4. Effective, Safe, & Rapid Reduction of Microfilarial Burdens
   - In the transplanted worm model mentioned in Study 1, it was shown that a combination of weekly ivermectin (6 mcg/kg) and daily doxycycline (10 mg/kg Q 24 H) eliminated microfilariae over 8 to 12 weeks.5
   - This elimination is relatively fast, but not so rapid that therapy results in the adverse, shock-like reactions seen with rapid destruction of large numbers of microfilariae. In addition, subacute removal of microfilariae lessens the chance of macrocyclic lactone resistance, especially when the practitioner is forced to use the slow-kill method due to owner finances or difficulty attaining adulticide (ie, melarsomine).

5. Reduced Lung Reaction to Worm Death (Spontaneous & Postadulticide)
   - Study 1 also showed that the combination of weekly ivermectin (6 mcg/kg PO) and daily doxycycline (10 mg/kg PO Q 24 H) significantly reduced lung lesions after melarsomine therapy.6,8

6. Developing Larva Eliminated
   - Recently, McCall, et al, demonstrated that, while doxycycline (even with ivermectin) does not have rapid adulticidal efficacy, doxycycline monotherapy does stop the progression of infective larvae to adulthood when administered for the first 30 days of infection at 10 mg/kg PO Q 24 H.9
   - If the 30 days of administration begin on day 40 of infection, however, the effect is partially lost, with...
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- If the larvae reach 65 days before doxycycline is initiated, only 52% reach adulthood.

Therefore, in addition to reducing adverse effects from heartworm death, doxycycline begun on the day of diagnosis will help close the potential seasonal window of continuous infection, which means that, during certain times of year when exposure is continuous (warmest months), the host may have developing larvae of all stages.

**Doxycycline Dosing**

Currently the best data we have argues that the dosage, if tolerated, is 10 mg/kg PO Q 12 H for 30 days, administered prior to adulticidal therapy (Figure 3). If this dose is not tolerated, it can be reduced to 5 mg/kg PO Q 12 H.

**Author Recommendation:** I advocate a second month's delay in adulticidal therapy to allow the parasite to deteriorate maximally and, thereby, further reduce the pulmonary reaction to worm death. Benefits include:

- Prevention of maturation of recently acquired infection (tissue phases)
- Reduced pulmonary reaction to dying worms
- More rapid and complete eradication of microfilariae (potentially reducing risk of heartworm resistance to macrocyclic lactones)

- Enhancement of vermicide efficacy of ivermectin, if using slow-kill method.

**AHS Recommendation:** The American Heartworm Society recommends that, if the slow-kill method is used (only out of necessity), doxycycline should be repeated in 60 days, so the dog receives ivermectin monthly and doxycycline 1 month on, 2 months off, 1 month on, 2 months off, etc, until the antigen test is negative. While there are no data that demonstrate the efficacy of this approach, there are data that indicate recruitment of Wolbachia by 300 days postdoxycycline.

In summary, it appears that doxycycline not only has a role in the management of heartworm infection, but that this role will continue to grow and be further refined.

**Figure Credits**

Figure 2. Courtesy Dr. Laura Kramer

Figure 3. Modified from Atkins CE, Miller MW. Is there a better way to administer heartworm adulticidal therapy? Vet Med 2003; 98:310-317.

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References