A Review of Study Designs and Outcomes of Phase I Clinical Studies of Nanoparticle Agents Compared with Small-Molecule Anticancer Agents

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Abstract

Purpose: Nanoparticles or carrier-mediated agents have been designed to prolong drug circulation time, increase tumor delivery, and improve therapeutic index compared to their small-molecule counterparts. The starting dose for phase I studies of small molecules and nanoparticles anticancer agents is based on the toxicity profile of the most sensitive species (e.g., rat or canine), but the optimal animal model for these studies of nanoparticles is unclear. The objective of this study was to evaluate the design, progression, and outcomes of phase I studies of nanoparticles compared with small-molecule anticancer agents.

Experimental design: In preclinical studies, the maximum tolerated dose (MTD) in rats and dogs was evaluated for nanoparticles and their respective small molecules. In phase I clinical trials in patients with advanced solid tumors, the basis for starting dose, the number of dose escalations, number of patients enrolled, and the ratio of MTD to starting dose was determined for nanoparticles and small molecules.

Results: The mean ratio of MTD to starting dose in clinical phase I studies was significantly greater for nanoparticles (13.9 ± 10.8) compared with small molecules (2.1 ± 1.1; P = 0.005). The number of dose levels in a clinical phase I study was also significantly greater for nanoparticles (7.3 ± 2.9) compared with small molecules (4.1 ± 1.5; P = 0.008).

Conclusions: The degree of dose escalation from starting dose to MTD was significantly greater for nanoparticles as compared with small-molecule anticancer drugs. These findings necessitate the need to identify the most appropriate preclinical animal model to use when evaluating nanoparticles toxicity. Clin Cancer Res; 19(12); 1–7. ©2013 AACR.

Introduction

Nanoparticles or carrier-mediated agents used to deliver anticancer therapies have many unique advantages over their traditional small-molecule counterparts, including improved solubility, longer circulation time, greater plasma exposure (AUC), tumor-selective delivery, increased antitumor response, and reduced toxicity (1, 2). The pharmacokinetics of nanoparticles is dependent upon the carrier and not the drug encapsulated within the carrier until the drug gets released from the carrier (2–5). The drug that remains encapsulated within nanoparticles, (generally >95%) or linked to a conjugate or polymer is an inactive produg, and thus the drug must be released from the carrier to be active. After the drug is released from the carrier, the pharmacokinetic disposition of the drug will be the same as that following administration of the noncarrier form of the drug (3, 4, 6). There is significant interpatient variability seen in the pharmacokinetics of nanoparticles, such as PEGylated liposomes, and the observed differences between patients could be attributed to heterogeneity in the mononuclear phagocyte system (MPS; refs. 7, 8). The MPS is composed of circulating monocytes and dendritic cells, as well as phagocytic cells in the liver and spleen (8).

The relationship between MPS and nanoparticle clearance (CL) was shown in a clinical phase I study using S-CKD602, a PEGylated liposomal camptothecin analog, in patients with refractory solid tumors (9). After administration of S-CKD602 there was a greater percentage decrease in monocytes (58 ± 34) versus absolute neutrophil count (42 ± 30) on 1 cycle of treatment (P = 0.001; ref. 9). There was also a linear relationship between percentage decrease in monocytes and the CL of encapsulated drug (R² = 0.75) and release of drug from the liposome (R² = 0.51; ref. 9). This relationship was not observed with the small-molecule formulation CKD-602. Therefore, unlike small molecules,
Translational Relevance

The degree of dose escalation from starting dose to MTD is significantly greater for nanoparticle compared with small-molecule anticancer drugs. This is associated with a significantly greater number of dose levels, time required to complete phase I studies, and costs to conduct phase I studies of nanoparticles. These findings necessitate the need to optimize the design of phase I studies of nanoparticle agents, particularly the identification of the most appropriate preclinical animal model to use when evaluating nanoparticle toxicity.

Materials and Methods

Study design

We evaluated differences in how phase I studies of nanoparticles and small molecules were designed and conducted. We evaluated the following factors related to phase I study designs for nanoparticles and small molecules: (i) ratio of MTD to starting dose; (ii) the number of dose escalations; (iii) the number of patients enrolled; (iv) time required to complete the study; and (v) total estimated cost of the study.

Using databases such as PubMed, Medline, and American Society of Clinical Oncology Proceedings, searches for peer reviewed phase I studies of nanoparticles and small molecules were conducted using the search terms: MTD, preclinical, phase I, pharmacokinetics, and toxicity. Data was collected for 9 nanoparticles and matching small-molecule anticancer agents. The nanoparticles were Abraxane (albumin-bound paclitaxel), NKTR-102 (PEGylated irinotecan), liposomal vincristine, OSI-211 (liposomal lurotenc), liposomal vinorelbine, NK-105 (PEGylated paclitaxel), S-CKD602 (PEGylated liposomal CKD-602), IHL-305 (PEGylated liposomal irinotecan), MBP-426 (PEGylated liposomal oxaliplatin; refs. 16–24). The small molecules were paclitaxel, irinotecan, lurotenc, vinorelbine, CKD-602, and oxaliplatin (25–28). The nanoparticle and small-molecule preclinical toxicology data was collected when available to determine the animal model used in defining starting dose in phase I clinical trials.

For preclinical studies, the MTD found in rats and dogs were recorded. For phase I studies in patients with advanced solid tumors, the starting dose, the number of dose escalations from starting dose to MTD, number of patients, and the ratio of MTD to starting dose were recorded for each nanoparticle and small molecule. The MTD reported in all studies was defined as 1 dose below the dose associated with the DLT. The DLT was defined as a grade 4 hematologic or grade 3/4 nonhematologic toxicity in all studies. The dose-escalation strategy for all of the reviewed phase I studies were conducted using the conventional 3+3 modified Fibonacci design (29). The methods used to determine the starting dose in the phase I study of the nanoparticles and small molecules were the same. As per standard methods, toxicology studies were conducted in rats and dogs. If rats were the most sensitive species, the starting dose in the phase I study was equal to one-tenth of the dose that was severely toxic to 10% of the animals on a mg/m² basis. If dogs were the most sensitive species, the starting dose in the phase I trial was equal to one-sixth of the highest nontoxic dose in the dog on a mg/m² basis.

Of 2 clinical phase I trials of nanoparticles and equivalent small molecules to evaluate whether significant differences existed in study design, progression, and outcomes between nanoparticles and small molecules. Nanoparticles comprise carrier-mediated platforms of anticancer agents, including liposomes and conjugates, which contain an active small molecule, whereas the small molecule includes cytotoxics and any non–nano anticancer agent excluding targeted therapies.
A cost estimation analysis was conducted to appraise the costs associated with a nanoparticles compared with a small molecule phase I study. Cost estimates were obtained from the literature and were based on the class (nanoparticles or small molecules) of agent, number of treatment levels, and patients (30).

Statistics

The null hypothesis was that there was no difference in the ratio of MTD to starting dose, dose escalations, and patients enrolled in a phase I clinical study between nanoparticles and small molecules. This was tested using a Student t test with α set at 0.05.

Results

Ratio of MTD to starting dose

The starting doses, MTD, and ratios of MTD to starting dose for each small molecule are shown in Table 1. For small molecules, the mean ± SD (range) of the ratio of MTD to starting dose was 2.1 ± 1.1 (1.3–4.0). The starting doses, MTD, and ratios of MTD to starting dose for each nanoparticles are shown in Table 2. For nanoparticles, the mean ± SD (range) of the ratio of MTD to starting dose was 13.9 ± 10.8 (2.2–37.7). The ratio of MTD to starting dose of nanoparticles was approximately 7-fold higher than small molecule (P = 0.005). For the nanoparticles, including NKT-102 (PEGylated irinotecan), liposomal vincristine (Marqibo), liposomal vinorelbine, NK-105 (PEGylated paclitaxel), S-CKD602 (liposomal CKD-602), and IHL-305 (PEGylated liposomal irinotecan), it was confirmed that the starting doses in clinical phase I studies were based on toxicology studies in dog (18–20, 22–24).

Dose escalations and number of patients

The dose-escalation strategy for all of the reviewed phase I studies were conducted using the conventional 3 + 3 modified Fibonacci design (29). There was an increase in the number of dose escalations and patients enrolled on phase I clinical study design and outcomes. There was a higher but not statistically different number of patients enrolled in a clinical phase I study of nanoparticles and small molecules (31.0 ± 9.3 and 25.1 ± 11.2, respectively; P = 0.16)

Cost estimation

The average cost per patient to complete a phase I clinical trial is approximately $35,000 (30). Assuming 3 patients per dose level based on the conventional 3 + 3 modified Fibonacci design, the cost of a small molecule or nanoparticle phase I clinical study would be $430,500 and $819,000, respectively. Excluding the nanoparticle agents that did not require an increased number of dose levels compared with their small-molecule counterpart brings the cost of a clinical phase I study of a nanoparticles to approximately $966,000. The rationale and justification of the removal is detailed within the Discussion section. Thus, a phase I clinical study of 2 identical chemical entities administered as a standard small molecule or within a nanoparticle formulation results in an approximately 2-fold difference in the overall costs.

Discussion

This is the first study or review highlighting major differences between nanoparticle and small molecule phase I clinical study design and outcomes. There was a significantly greater number of dose levels, time required to complete phase I studies, and costs to conduct phase I studies of nanoparticles compared with small molecules. These results indicate the inefficiency in which phase I studies of nanoparticles are designed and/or carried out relative to small molecules. The cause of observed differences in clinical phase I studies may be due to differences in the pharmacokinetics and pharmacodynamics of nanoparticles, preclinical animal models used for toxicities of nanoparticles are listed in Tables 1 and 2, respectively. The mean ± SD (range) number of dose levels in a phase I clinical study for nanoparticles and small molecules were 7.8 ± 2.9 (4–13) and 4.1 ± 1.5 (3–7), respectively (P = 0.008). A summary of mean ± SD (range) of MTD to starting dose, number of dose levels, and number of patients enrolled is provided in Table 3. There was a higher but not statistically different number of patients enrolled in a clinical phase I study of nanoparticles and small molecules (31.0 ± 9.3 and 25.1 ± 11.2, respectively; P = 0.16).

Table 1. Summary of starting dose, MTD, and ratio of MTD to starting dose in patients with refractory solid tumors in phase I clinical trials of small-molecule anticancer agents

<table>
<thead>
<tr>
<th>Small molecule</th>
<th>Starting dose (mg/m²)</th>
<th>MTD (mg/m²)</th>
<th>Ratio of MTD to starting dose</th>
<th>Total number of dose levels</th>
<th>Total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>0.5</td>
<td>0.75</td>
<td>1.5</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>240</td>
<td>320</td>
<td>1.3</td>
<td>4</td>
<td>34</td>
</tr>
<tr>
<td>OKD–602</td>
<td>0.5</td>
<td>0.7</td>
<td>1.4</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>70</td>
<td>100</td>
<td>1.4</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>35</td>
<td>40</td>
<td>1.1</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>45</td>
<td>135</td>
<td>3.0</td>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td>Lurtotecan</td>
<td>0.3</td>
<td>1.2</td>
<td>4.0</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Mean ± SD (range)</td>
<td>2.0 ± 1.1 (1.1–4)</td>
<td>4.1 ± 1.5 (3–7)</td>
<td>25.1 ± 11.2 (13–44)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
nanoparticles, or study design issues of nanoparticles compared with small molecules.

The pharmacokinetics of nanoparticles is more variable than small molecules. A meta-analysis compared differences in AUC CV% as a measure of variability between liposomal and nonliposomal anticancer agents (31). For liposomal agents, the mean ± SD of CV% of AUC was 65.6 ± 18.6. For nonliposomal agents, the mean ± SD of CV% of AUC was 30.7 ± 16.0. The ratio of liposomal to non-liposomal CV% of AUC for each pair was 2.7 (P < 0.001; Eq 1).

Similarly, the mean ± SD ratio of AUCmax to AUCmin at the MTD was 34.1 ± 41.9 for liposomes and 3.6 ± 1.8 for non-liposomal drugs. The ratio of liposomal to non-liposomal ratio of AUCmax to AUCmin for each pair was 16.7 (P<0.13). The significantly higher and clinically relevant pharmacokinetic variability of nanoparticles compared with small molecules may be affecting the design and progression of Phase I studies of nanoparticles agents. Thus, studies need to be conducted and methods developed to evaluate and predict the factors inducing the high pharmacokinetics and pharmacodynamic variability of nanoparticles (32–34).

A potential reason for the discrepancy between nanoparticles and small molecules in human phase I studies could be model selection in preclinical studies. When allometric scaling was used to compare the pharmacokinetic disposition of three different PEGylated liposomes (S-CKD602, Doxil, SPI-077) across species (mice, rats, dogs, and humans) at the MTD, the pharmacokinetic disposition in dogs was a consistent outlier from other animal models (15). In addition, when a Dedrick Time Equivalent model was used, dogs had the highest CL and thus the lowest exposure of all 3 liposomal agents at the MTD (15). This suggests that dogs clear PEGylated liposomes faster than other species which results in a lower plasma exposure but are the more sensitive to nanoparticles toxicity at this lower exposure. Thus, using dogs to determine starting dose in man results in a dose that is lower than needed and consequently creates exposures that have a low probability of achieving response and/or inducing toxicity. This results in an increase in the number of dose levels, number of patients, and ratio of MTD to starting dose for nanoparticles compared with small molecules. Physiologically based pharmacokinetic modeling and allometric scaling have been previously used for many small-molecule agents to predict human pharmacokinetics from animal data. Mahmood reported on the MTD of 25 small-molecule anticancer drugs that could be used to predict the proper starting dose in humans (35). He concluded that the approach saves

### Table 2. Summary of starting dose, MTD, and ratio of MTD to starting dose in patients with refractory solid tumors in phase I clinical trials of nanoparticle anticancer agents

<table>
<thead>
<tr>
<th>Carrier-mediated agent (NP)</th>
<th>Starting dose (mg/m²)</th>
<th>MTD (mg/m²)</th>
<th>Ratio of MTD to starting dose</th>
<th>Total number of dose levels</th>
<th>Total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin-bound paclitaxel</td>
<td>135</td>
<td>300</td>
<td>2.2</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>NKTR-102 (PEGylated irinotecana)</td>
<td>58</td>
<td>144</td>
<td>2.5</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>Liposomal vincristine</td>
<td>0.5</td>
<td>2.4</td>
<td>4.8</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>OSI-211 (liposomal lurtotecan)</td>
<td>0.15</td>
<td>1.8</td>
<td>12.0</td>
<td>7</td>
<td>37</td>
</tr>
<tr>
<td>Liposomal vinorelbinea</td>
<td>2</td>
<td>28</td>
<td>14.0</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>NK-105 (PEGylated paclitaxela)</td>
<td>10</td>
<td>180</td>
<td>18.0</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>S-CKD602 (PEGylated liposomal CKD-602a)</td>
<td>0.1</td>
<td>2.1</td>
<td>21.0</td>
<td>13</td>
<td>45</td>
</tr>
<tr>
<td>IHL-305 (PEGylated liposomal irinotecana)</td>
<td>7</td>
<td>160</td>
<td>22.9</td>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td>MBP-426 (PEGylated liposomal oxaliplatin)</td>
<td>6</td>
<td>226</td>
<td>37.7</td>
<td>11</td>
<td>39</td>
</tr>
<tr>
<td>Mean ± SD (range)</td>
<td>13.9 ± 10.8 (2.2–37.7)</td>
<td>7.8 ± 2.9 (4–13)</td>
<td>31.8 ± 9.5 (19–45)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aConfirmed starting doses in clinical phase I studies were based on toxicology studies in dog.

### Table 3. Comparison of ratio of MTD to starting dose, number of dose levels, and number of patients enrolled on study for clinical phase I studies of nanoparticle and small-molecule anticancer agents

<table>
<thead>
<tr>
<th></th>
<th>Ratio of MTD to starting dose</th>
<th>Number of dose levels</th>
<th>Total number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP Mean ± SD (range)</td>
<td>13.9 ± 10.8</td>
<td>7.8 ± 2.9</td>
<td>31.8 ± 9.5</td>
</tr>
<tr>
<td>SM Mean ± SD (range)</td>
<td>2.0 ± 1.1</td>
<td>4.1 ± 1.5</td>
<td>25.1 ± 11.2</td>
</tr>
<tr>
<td>Comparison of NP vs. SM; 2 sample t test</td>
<td>P = 0.005</td>
<td>P = 0.008</td>
<td>P = 0.16</td>
</tr>
</tbody>
</table>

Abbreviations: NP, nanoparticle; SM, small molecule.
time and avoids many unnecessary steps in attaining the MTD in humans. This information is in contrast to nanoparticles, which are not extensively metabolized, have greater pharmacokinetic variability compared with small molecules, and the pharmacokinetics in animal models is not directly extrapolated to humans. (15).Although animal models have successfully predicted small-molecule pharmacokinetics in humans in prior studies, the ability to predict nanoparticle pharmacokinetics in humans based on results in animal models seems to be more problematic. The inability to extrapolate nanoparticle pharmacokinetics to patients from animal models is most likely due to differences in the MPS across species. Thus, the standard models and methods used for small molecules cannot be used for nanoparticles. Future studies are needed to determine the most appropriate animal model and scaling methods for nanoparticles.

Another potential reason for an increased number of dose levels could be that nanoparticles have a lower toxicity than small molecules and therefore the dose of nanoparticles can be escalated to higher levels than small molecules. In vitro and preclinical studies have shown that the toxicity of PEGylated liposomal agents and other nontargeted nanoparticles carriers is less than the comparative small molecule (3, 36, 37). For example, the cytotoxicity of mitomycin C was drastically reduced when prepared in PEGylated liposomes (38). It also has been clinically noted that the biodistribution pattern of liposomes can lead to a relative reduction of drug concentrations in tissues that are known to be sensitive to the drug (39). The biodistribution pattern is due to the unique pharmacokinetic profile that is obtained after administration of nanoparticles, such as increased plasma exposure (AUC) and reduced CL of the inactive-encapsulated drug (3, 22). Generally, stable nanoparticles carriers have minimal drug release in the circulation which reduces toxicities in normal organs (3, 22).

Of the nanoparticles 9 agents reviewed, 4 studies stated that the starting dose was based on dogs within the clinical phase I study. One study (Abraxane) stated that dogs had a hypersensitivity reaction to the nanoparticles and the in the remaining 4 studies, no information was provided on the starting dose. There were 3 nanoparticle that did not follow the trend of greater resources and time to complete the phase I study (e.g., greater ratio of MTD to starting dose) compared with small molecule. Those were nanoparticles were liposomal vincristine, albumin-bound paclitaxel (Abraxane), and liposomal irinotecan. These agents all exhibit "nonclassical" nanoparticles properties and interesting aspects of their preclinical and clinical results provide rationale for why they can be removed from the analysis.

A study conducted by Zhigaltsev and colleagues, compared drug loading and retention among liposome-encapsulated vinca alkaloids: vincristine, vinblastine, and vinorelbine (40). While vincristine had the greatest percentage of drug retention after a single dose of the 3 tested vinca alkaloids, it had only approximately 56% or 78% drug retention after 24 hours for the 0.1 w/wt and 0.3 wt/wt drug-to-lipid ratio formulations, respectively. This finding is in contrast to preclinical and clinical in vivo data of other liposomal anticancer agents which have a much greater percentage of (i.e., 90%–95%) drug retention during the first 24 hours and beyond (22, 41). One of the most compelling examples of low vincristine retention in liposomes comes from a study conducted by Sapra and colleagues, whose objective was to find an effective strategy for treating B-cell malignancies in a murine model of human B-cell lymphoma (42). Long-circulating sterically stabilized immunoliposome formulations of vincristine and doxorubicin were given to these mice. The liposomal vincristine formulation had a much faster drug release rate from the liposomes than liposomal doxorubicin. In addition, after normalization of drug load to lipid amount, the drug to lipid ratio was several fold higher for liposomal doxorubicin than for liposomal vincristine over a 48-hour period (42). Thus, the liposomal vincristine included in this review seems to have rapid CL and release of drug from the carrier and thus does not exhibit classic nanoparticle properties of prolonged circulation of encapsulated drug that is cleared by the MPS. Instead, the vincristine is rapidly released from the liposome and cleared via hepatic metabolism and thus acts more like a small-molecule agent than the other nanoparticles included in this review.

The pharmacokinetics and pharmacodynamics of IHL-305 were also different than other nanoparticles. IHL-305 is a PEGylated liposome formulation of CPT-11. CPT-11 is a prodrug that must be converted to the active moiety SN-38 by carboxylesterase enzymes in vivo (43). The complexity of CPT-11 metabolism goes further, to include active lactone and inactive carboxylate forms of both the CPT-11 and SN-38, which exist at an equilibrium dependent upon pH and binding proteins (44). The complexity of metabolism increases with the involvement of genetic polymorphisms in uridine diphosphate glucuronosyltransferases (UGT) isofrom 1A1, (UGT1A1), which is responsible for glucuronidation of SN-38 (45). Therefore, it is unclear whether differences in phase I outcomes are observed due to IHL-305 formulation, or due to the dosing of a prodrug that is dependent upon many factors for metabolism.

The phase I starting dose of albumin-bound paclitaxel was not based on the dog toxicology studies because dogs had a hypersensitivity reaction to human albumin which lead to an early termination of toxicologic studies in dogs (46). Therefore, the starting dose of albumin-bound paclitaxel was based on toxicology studies in nonhuman primates. Dogs seem to be inherently sensitive to the toxicologic effects of nanoparticles, as evidenced through toxicology studies as well as allometric scaling (15). The starting dose of albumin-bound paclitaxel based on toxicity studies in nonhuman primates was most likely higher than would have been determined on the basis of toxicology studies in dogs. Thus, the number of dose levels from the higher starting dose to the MTD of albumin-bound paclitaxel was less than other nanoparticles in the review. This highlights the potential benefits of conducting toxicologic and pharmacologic studies of nanoparticles in nonhuman primates instead of dogs as the nonrodent species of choice.
There are major differences between the design and performance of phase I studies of nanoparticles compared with small molecules. There is a significant difference in the number of dose levels and ratio of MTD to starting dose as well as increased number of patients enrolled and overall costs associated with studies of nanoparticles versus small molecules. These findings indicate that patients are being treated at doses that are very low and unlikely to produce toxicity and/or response. This undoubtedly leads to an inefficient use of patient resources, time, and funding. The potential primary cause of these issues in phase I studies of nanoparticles is that the low starting dose results from the use of an inappropriate toxicology model, which seems to be dogs or the ability to escalate the dose of nanoparticles higher. An alternative nonrodent model such as nonhuman primates may be more suitable.

There is preliminary evidence that suggests that factors associated with the MPS may contribute to nanoparticles pharmacokinetic and pharmacodynamic variability. Thus, there is a compelling need to identify the factors associated with MPS function to improve the preclinical and clinical studies of nanoparticles. It will be essential to further test whether the pharmacokinetics of nanoparticles can be scaled across species using various measurements and surrogates of the MPS, such as monocyte and macrophage activity or function, genetics, complement, or cytokines. In addition, the most appropriate animal models for GLP toxicology studies must be identified. Identification of the correct animal model may drastically decrease the number of dose levels, patients, and costs associated with phase I clinical studies. In addition, there must be exploitation into new study designs for phase I studies of nanoparticles, as the unique pharmacology of nanoparticles agents may not be amenable to trial designs established for small molecules.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Authors’ Contributions**

Conception and design: K.P. Morgan  
Development of methodology: K.P. Morgan  
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W.P. Caron, K.P. Morgan, W. Zamboni  
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): W.P. Caron, K.P. Morgan, W. Zamboni  
Writing, review, and/or revision of the manuscript: W.P. Caron, K.P. Morgan, B.A. Zamboni  
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K.P. Morgan

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