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Timing and Course of Clinical Response to Intravenous Immunoglobulin in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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Timing and Course of Clinical Response to Intravenous Immunoglobulin in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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Objective: To investigate the timing, course, and clinical characteristics of the response to intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Design: Data were extracted from the ICE trial, a randomized, double-blind, placebo-controlled trial of immune globulin intravenous, 10% caprylate/chromatography purified (IGIV-C).

Setting: Multiple international centers.

Participants: One hundred seventeen individuals with CIDP.

Intervention: Treatment with IGIV-C (Gamunex, n=59) or placebo (n=58), with IGIV-C administered as a 2-g/kg loading dose followed by a 1-g/kg maintenance dose every 3 weeks, for up to 24 weeks.

Main Outcome Measures: The primary efficacy parameter was an improvement of 1 or more points in adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score. Participants treated with IGIV-C were divided into subgroups based on meeting responder vs non-responder definitions and by time to first improvement.

Results: Among 30 responders to IGIV-C, 14 (47%) patients had improved adjusted INCAT scores by week 3, and 16 (53%) patients improved at week 6 after a second infusion. Participants who improved by week 3 were more severely disabled at baseline than those who improved at 6 weeks. In patients who improved, the number of individuals reaching maximal improvement continued to increase during maintenance therapy for up to 24 weeks. For patients with first improvement by week 3, the change in dominant-hand grip strength over time tended to parallel the INCAT score. In patients with first improvement by week 6, however, the improvement in dominant-hand grip strength preceded initial improvement in INCAT score.

Conclusions: Data suggest that treatment with 2 courses of IGIV-C administered 3 weeks apart may be required for initial improvement, and continued maintenance therapy may be necessary to achieve a maximal therapeutic response.

Trial Registration: clinicaltrials.gov Identifier: NCT00220740

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CHRONIC INFLAMMATORY demyelinating polyradiculoneuropathy (CIDP) is an autoimmune disease that targets the myelin sheaths of the peripheral nerves.^{1,2} Intravenous immunoglobulin (IVIg) has



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Group Information: The ICE Study Group members are listed at the end of this article.

been shown to be effective for the treatment of CIDP.³ However, published studies have not provided detailed information on the timing or characteristics of the

clinical response to IVIg therapy, and only 1 small study (N=53)⁴ has evaluated the response to administration of more than a single dose of IVIg vs placebo for treating CIDP. Thus, it has been unclear whether patients will achieve an initial response with a single IVIg dose or what the benefit of additional doses might be. To help answer these questions, we conducted a post hoc analysis of the data from the largest trial of IVIg in CIDP published to date, the IGIV-C CIDP Efficacy (ICE) trial (n=117),⁵ to determine the time to initial response, the duration of treatment needed to achieve maximal improvement in clinical disability, and the characteristics of the clinical response.

PATIENTS AND PROCEDURE

The ICE trial was a randomized, multicenter, double-blind, response-conditional cross-over trial of immune globulin intravenous, 10% caprylate/chromatography purified (IGIV-C; Gamunex, Talecris Biotherapeutics, Research Triangle Park, North Carolina) vs placebo (0.1% albumin). The study was approved by the institutional review boards and ethics committees of all participating centers, and all patients provided written informed consent. Details on the study design, patient population, and methodology have been described previously.^{5,6} In the first period of the trial, participants with CIDP received a baseline IGIV-C loading dose of 2 g/kg administered over 2 to 4 days, followed by a maintenance dose of 1 g/kg every 3 weeks for up to 24 weeks. Participants were evaluated at day 16 and at 3-week intervals thereafter. The primary efficacy parameter was response, defined as an improvement of 1 or more points in the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score. Responders were defined as patients who showed an improvement from baseline of 1 or more points in the adjusted INCAT disability score that was maintained through to the final measurement at week 24. Participants whose adjusted INCAT disability score deteriorated by 1 or more points at any visit after the first infusion, did not improve by week 6, or improved but then decreased to or below baseline at any time at or after week 6 were moved over to the rescue phase of the study and were considered nonresponders.

Additional end points analyzed included dominant-hand grip strength, INCAT sensory sum score, Medical Research Council (MRC) sum score, and the mean compound muscle action potential amplitude in motor nerves. Grip strength was determined at each visit; INCAT sensory sum scores, MRC sum scores, and the mean compound muscle action potential amplitude were measured at baseline and the final visit.

Median, ulnar, peroneal, and tibial motor nerves were tested, and peak-to-peak motor amplitudes were measured. The median motor nerve was tested using stimulation at the wrist, elbow, axilla, and Erb point (optional); the ulnar motor nerve was tested using stimulation at the wrist, above the elbow, the axilla, and the Erb point; the peroneal motor nerve was tested using stimulation at the ankle, below the fibular head, and at the lateral popliteal fossa; and the tibial motor nerve was tested using stimulation at the ankle and popliteal fossa. The MRC sum score assessed 12 muscles—3 arm and 3 leg muscles on both body sides. These muscles were the deltoid (shoulder abduction), biceps (elbow flexion), wrist extensor, iliopsoas (hip flexion), quadriceps femoris (knee extension), and tibialis anterior (ankle dorsiflexion).

STATISTICAL ANALYSIS

Participants treated with IGIV-C were divided into 4 subgroups based on meeting the definition of a responder vs a nonresponder and also by time to first improvement (improvement of ≥ 1 points in the adjusted INCAT disability score): group A included IGIV-C responders who first improved by week 3; group B included IGIV-C responders who first improved by week 6; group C included IGIV-C nonresponders who had no change in adjusted INCAT disability score (ie, stable) at week 6; and group D included IGIV-C nonresponders who had a worsening of 1 or more points in the adjusted INCAT disability score at or before week 6. In addition, patients treated with placebo who were classified as responders were divided into subgroups: placebo responders who first improved by week 3 (group E) and placebo responders

who first improved by week 6 (group F). Participants who had responses after week 6 were not included in the analysis.

A univariate logistic regression model was used for the comparisons between groups. If a complete separation or a quasi-complete separation of data points occurred, a group *t* test was used. Two-tailed $P < .05$ was considered statistically significant. Version 9.1 of SAS was used for all statistical analyses. Owing to the exploratory nature of the analyses, no adjustment for multiplicity was performed.

RESULTS

In the ICE trial, 32 of 59 (54%) participants treated with IGIV-C were identified as responders vs 12 of 58 (21%) participants receiving placebo ($P < .001$).⁵ Responders achieved an improvement from baseline of at least 1 point in the adjusted INCAT disability score by week 6 that was maintained through to the final measurement at week 24. Among these responders, 14 of 32 (44%) patients in the IGIV-C group and 7 of 12 (58%) in the placebo group responded by week 3 ($P = .73$). The remaining 27 of 59 patients in the IGIV-C group and 46 of 58 patients in the placebo group were considered nonresponders. Of the 27 nonresponders in the IGIV-C group, 13 remained stable, 8 worsened by 6 weeks, and 6 improved transiently but then deteriorated and crossed over to alternate (rescue) treatment.

Fourteen of the 59 (24%) IGIV-C-treated participants responded by week 3 (group A), and an additional 16 (27%) IGIV-C-treated participants responded by week 6 (group B). Two responders in the IGIV-C group who were stable at week 6 and should have crossed over to the alternate treatment did not cross over at the request of their physician. These 2 responders showed improvement in adjusted INCAT disability score at weeks 12 and 18 and were not included in the current analyses. In the placebo group, 7 of 58 (12%) participants improved by week 3, and an additional 5 (9%) participants improved by week 6.

To assess potential differences among participants responding to IGIV-C, baseline characteristics were compared among various subgroups (Table 1). Group A, IGIV-C responders who improved by week 3, exhibited more severe disease at baseline than IGIV-C responders who improved by week 6, with group A having a statistically significantly higher mean baseline INCAT disability score (5.4 vs 3.9; $P = .02$) and lower MRC sum score (45.5 vs 50.9; $P = .04$). Additional mean baseline efficacy measures also suggested greater severity in group A vs group B, but the differences were not statistically significant; there were no significant differences in baseline demographics. Group C, IGIV-C nonresponders who remained stable at week 6, had a significantly lower mean baseline INCAT disability score and a higher MRC sum score than group A and had a lower INCAT disability score than group D, IGIV-C nonresponders who had a worsening in INCAT disability score by week 6.

Although baseline data indicated that group A had more severe disease than group B, group A experienced a statistically significantly greater improvement from baseline in the mean adjusted INCAT disability score and in the averaged compound muscle action potential amplitudes at the end of the first period (ie, at 24 weeks; Table 2). There were no significant differences be-

Table 1. Baseline Characteristics of Study Sample

Baseline Characteristic	Mean (SD) by Treatment and Group					
	IGIV-C			Placebo		
	Group A (n=14) ^a	Group B (n=16) ^b	Group C (n=13) ^c	Group D (n=8) ^d	Group E (n=7) ^e	Group F (n=5) ^f
Age, y	47.0 (16.2)	46.5 (18.2)	56.3 (15.9)	52.9 (19.8)	48.3 (19.8)	60.8 (23.6)
Sex, %						
M	42.9	56.3	69.2	37.5	71.4	80.0
F	57.1	43.8	30.8	62.5	28.6	20.0
Time since initial CIDP symptoms, y	4.9 (8.0)	6.0 (5.8)	8.2 (10.3)	4.7 (6.1)	1.4 (1.7) ^g	11.5 (6.2) ^g
Time since CIDP diagnosis, y	2.1 (4.0)	2.6 (2.6)	1.9 (3.1)	2.7 (5.2)	0.2 (0.4)	2.0 (3.8)
INCAT disability score	5.4 (1.5) ^{h,l}	3.9 (1.3) ^h	3.4 (0.9) ^l	4.6 (1.4)	4.7 (2.1)	3.6 (1.1)
MRC sum score	45.5 (7.8) ^j	50.9 (4.8) ^j	50.8 (5.1)	49.8 (8.5)	53.0 (6.7)	55.2 (2.4)
Dominant-hand grip strength, kPa	42.1 (22.5)	46.5 (28.8)	51.9 (18.1)	54.4 (30.5)	58.6 (18.5)	50.2 (13.9)
ISS score	8.8 (6.3)	7.7 (4.1)	7.0 (3.5)	5.4 (6.0)	6.6 (4.9)	10.0 (5.1)
Mean CMAP amplitude, mV	3.3 (1.6)	4.4 (2.7)	3.5 (1.7)	3.5 (2.1)	4.6 (1.9)	3.2 (2.5)

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMAP, compound muscle action potential; IGIV-C, immune globulin intravenous, 10% caprylate/chromatography purified; INCAT, Inflammatory Neuropathy Cause and Treatment; ISS, INCAT sensory sum; MRC, Medical Research Council.

^a Responders to IGIV-C who first improved by week 3.

^b Responders to IGIV-C who first improved by week 6.

^c Nonresponders who had no change in adjusted INCAT disability score (ie, stable) at week 6.

^d Nonresponders who had a worsening of 1 or more points in adjusted INCAT disability score at or before week 6.

^e Responders to placebo who first improved by week 3.

^f Responders to placebo who first improved by week 6.

^g $P=.002$, group E vs group F (determined by group *t* test).

^h $P=.02$, group A vs group B.

ⁱ $P=.01$, group A vs group C.

^j $P=.04$, group A vs group B.

Table 2. Change From Baseline to the End of the Study in Clinical Efficacy Parameters

Measure	IGIV-C			Placebo		
	Mean (SD) Change		P Value	Mean (SD) Change		P Value
	Group A ^a (n=14)	Group B ^b (n=16)		Group E ^c (n=7)	Group F ^d (n=5)	
Adjusted INCAT disability score	-3.2 (2.2)	-1.5 (0.8)	.02	-3.3 (1.2)	-1.2 (0.4)	.006 ^e
Dominant-hand grip strength, kPa	24.0 (22.4)	20.0 (19.5)	.60	17.0 (19.0)	4.2 (8.7)	.20
MRC sum score	6.4 (8.2)	4.9 (3.8)	.53	5.0 (5.7)	3.0 (3.7)	.47
ISS score	-2.3 (4.2)	-1.0 (2.7)	.31	-1.1 (5.2)	-2.8 (6.5)	.60
Mean CMAP amplitude, mV	2.3 (2.0)	0.8 (0.7)	.03	1.4 (3.8)	-0.03 (1.3)	.44

Abbreviations: CMAP, compound muscle action potential; IGIV-C, immune globulin intravenous, 10% caprylate/chromatography purified; INCAT, Inflammatory Neuropathy Cause and Treatment; ISS, INCAT sensory sum; MRC, Medical Research Council.

^a Responders to IGIV-C who first improved by week 3.

^b Responders to IGIV-C who first improved by week 6.

^c Responders to placebo who first improved by week 3.

^d Responders to placebo who first improved by week 6.

^e Determined by group *t* test.

tween the 2 groups in changes from baseline for the other clinical efficacy parameters analyzed.

Comparing the placebo responder subgroups, we found that there were no statistically significant differences in baseline demographics or characteristics, with the exception of time since initial CIDP symptoms (Table 1). At the end of the study period (ie, 24 weeks), placebo responders who first improved by week 3 showed a statistically significantly greater improvement in the adjusted INCAT disability score compared with placebo responders who first improved by week 6 (Table 2). There were no significant differences from baseline between the 2 groups in the other clinical efficacy parameters analyzed.

To determine when IGIV-C responders achieved maximal improvement during the 24-week treatment period, the time to reach maximal improvement on the INCAT disability score was examined in patients who responded by week 3 (group A) or by week 6 (group B). Time to maximal improvement was also examined in patients receiving placebo who first improved by week 3 (group E) or week 6 (group F). As shown in Figure 1, of patients who improved, the number of patients reaching maximal improvement continued through week 24 in both the IGIV-C and placebo groups.

When comparing changes in the INCAT disability score to grip strength over time (Figure 2), we found that pa-

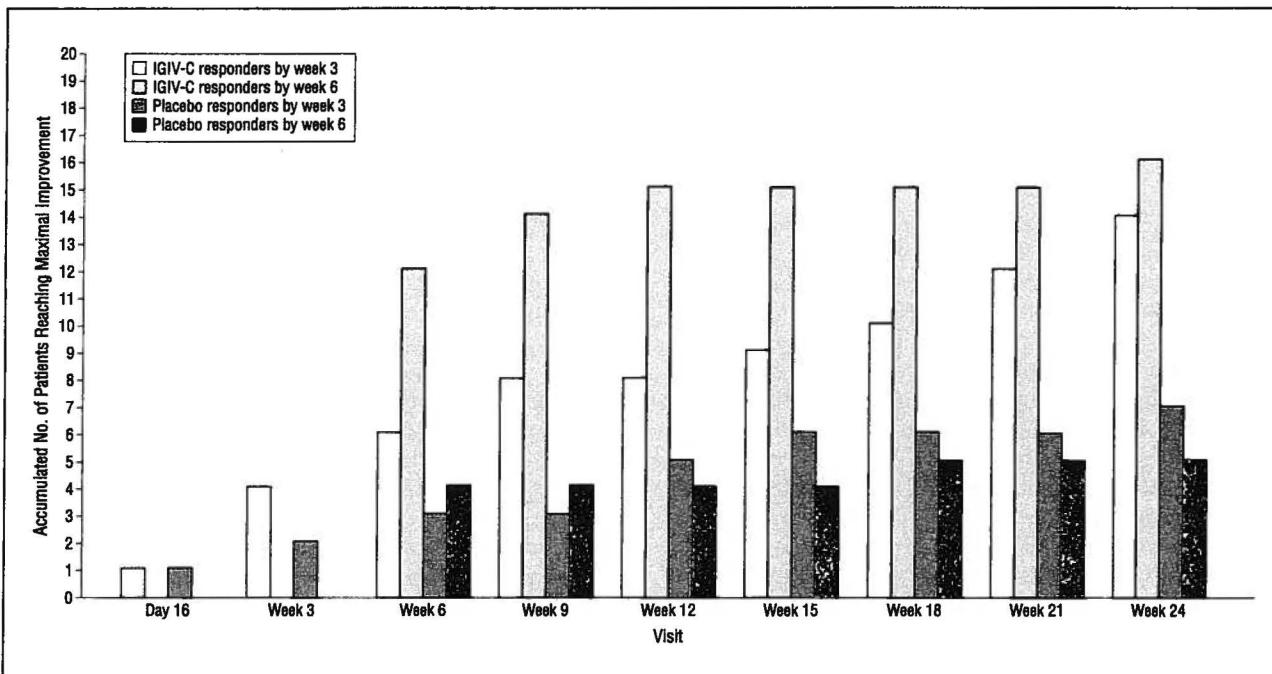


Figure 1. Responders who reached maximal improvement. Cumulative number of responders in immune globulin Intravenous, 10% caprylate/chromatography purified (IgIV-C) and placebo groups reaching maximal adjusted Inflammatory Neuropathy Cause and Treatment score improvement.

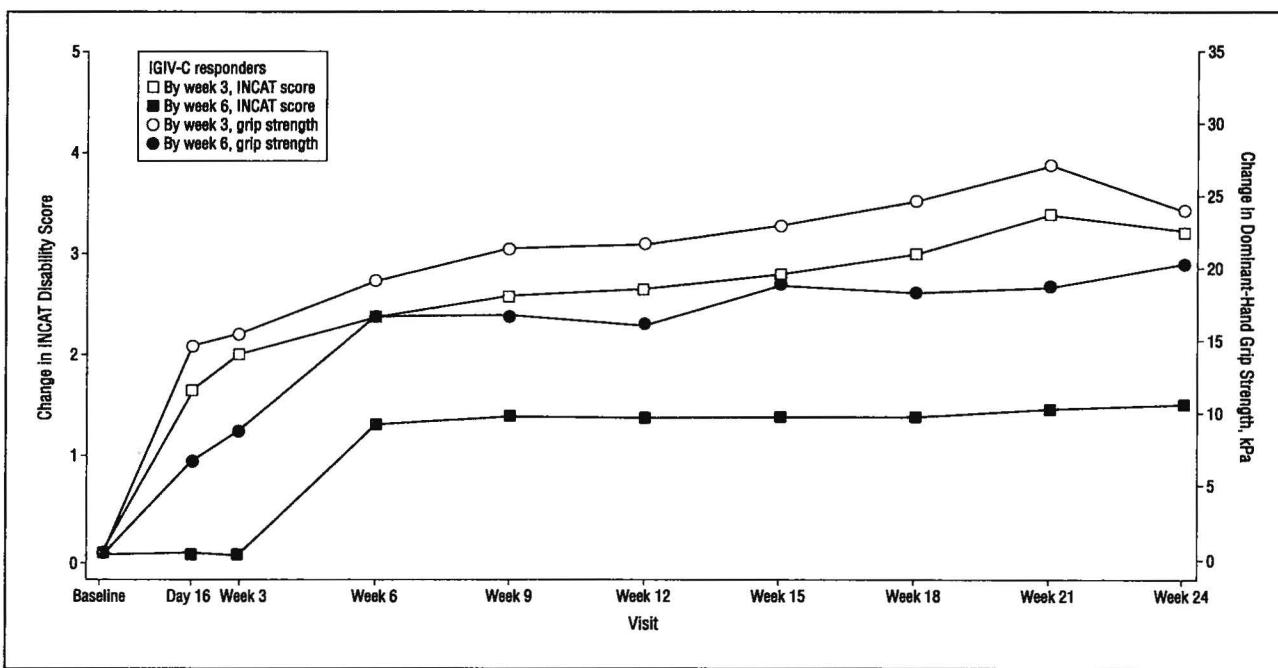


Figure 2. Mean change in adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) score and grip strength. Mean change from baseline for immune globulin Intravenous, 10% caprylate/chromatography purified (IgIV-C) responders.

tients in both groups A and B exhibited a statistically significant improvement in dominant-hand grip strength compared with baseline at week 3 and at week 6. For groups A and B, the mean improvement from baseline in dominant-hand grip strength at 3 weeks was 15.4 kPa (SD, 15.1 kPa; $P = .002$) and 8.5 kPa (SD, 12.7 kPa; $P = .02$), respectively, and at 6 weeks was 19.1 kPa (SD, 16.1 kPa; $P < .001$) and 16.2 kPa (SD, 17.3 kPa; $P = .003$), respectively. For patients in group A, the change in grip strength over time tended to parallel the INCAT disability score

(Figure 2). In patients in group B, however, improvement in dominant-hand grip strength preceded initial improvement in adjusted INCAT disability score.

COMMENT

In the ICE trial, 30 participants in the IgIV-C group improved by at least 1 point in the adjusted INCAT disability score during the initial 6 weeks of the study after 2

infusions of IGIV-C. Further examination of the data revealed that 14 participants responded by week 3 and another 16 responded by week 6 after the second course of IGIV-C treatment. These findings are consistent with findings from a smaller study by Mendell et al⁴ in which some patients initially improved after a second IVIg dose. Because the ICE trial design required participants to cross over to alternate therapy (rescue) if they had not improved by week 6 (ie, 2 dose courses), it is unknown whether more participants would have improved with additional IGIV-C treatments. These observations suggest that patients should be treated with at least 2 courses of IGIV-C (6-week time frame) to determine whether they are responding to treatment. Additional studies would be needed to determine whether patients who did not respond to 2 IGIV-C treatments or those whose condition stabilized would benefit from additional treatments.⁷

Of those who responded to IGIV-C, participants with greater disability (as determined by the baseline adjusted INCAT disability score) responded to IGIV-C therapy more rapidly and vigorously than those who were less severely affected. The reasons for these differences are unclear; they could be related to fundamental differences between the 2 patient groups or to differences in sensitivities of particular ranges within the same or between different clinical efficacy measures. The adjusted INCAT disability scale, for example, may be less sensitive to change at its lower range, possibly explaining the delay or lack of response in the less severely disabled patients in group B, when compared with the earlier observed improvement of grip strength.

Comparing the characteristics of response during therapy in this post hoc analysis, we found that dominant-hand grip strength tended to parallel or precede initial improvement in INCAT disability score. Given that grip strength is a simple assessment tool, it might be a more useful marker of initial response to therapy in clinical practice vs the INCAT disability scale. Additional studies are worthwhile to ascertain whether determination of grip strength would be a useful measure of response in routine clinical practice. Regardless of which of these 2 characteristics were evaluated, improvement was maintained in responders.

A small number of participants in the placebo group showed a similar pattern of response to that observed in the IGIV-C group, which, however, did not always reach statistical significance. Possible explanations include a limited response to the albumin mixture in the placebo treatment or the occurrence of spontaneous remission, which may occur in CIDP.¹ Once the inflammatory reaction subsides, the course of improvement might depend more on the rate of nerve recovery or regeneration than on the cause, with a similar course in treated or spontaneously remitting patients. Further investigation of these issues might help the selection of appropriate clinical efficacy measures and patient populations in future clinical trials.

Participants actively treated with IGIV-C continued to improve for variable periods, and once maximal response was achieved, it was maintained with treatment every 3 weeks. Although some patients' conditions may stabilize or improve after therapy is discontinued,⁸ a re-

lapse rate of approximately 45% was noted in the ICE Study for responders who were switched from IGIV-C to placebo.⁵ Therefore, discontinuing IVIg treatment before maximal improvement in CIDP is achieved may deprive patients of the full therapeutic benefit.

Optimal treatment of CIDP would prevent relapses with accompanying nerve damage that can cause disability.^{9,10} Patients with CIDP may therefore benefit from more than 1 treatment course with IGIV-C across 6 weeks to determine whether there is a response, and additional treatments may be required to achieve and maintain a maximal clinical response.

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Role of the Sponsor: The study sponsors designed the trial, interpreted the data, and provided editorial support for preparation of the manuscript in consultation with the steering committee. The authors had full access to all the data and made the final decision to submit the manuscript for publication. Statistical analyses were conducted by Dr Deng, Talecris Biotherapeutics. In addition, the statistical methods and results presented in this article were reviewed by Danyu Lin, PhD, University of North Carolina at Chapel Hill, Chapel Hill. Dr Lin's suggestions were incorporated into the article. Dr Lin was compensated for review of the manuscript and has no additional financial ties to Talecris Biotherapeutics.

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