

IN THE UNITED STATES COURT OF FEDERAL CLAIMS

OFFICE OF SPECIAL MASTERS

WALTER RAY GRAVES and LISA GRAVES
as representatives of the estate of
HAYLEY NICOLE GRAVES, deceased,

Petitioners,

v.

SECRETARY OF HEALTH
AND HUMAN SERVICES,

Respondent.

No. 02-1211V
Senior Judge James F. Merow
Special Master Christian J. Moran

Filed: September 21, 2010

entitlement, remand, Prevnar,
seizures without fever, significant
aggravation, death, dose-dependent
response

Richard Gage, Esq., Richard Gage, P.C., Cheyenne, WY., for Petitioners;
Lisa A. Watts, Esq., United States Department of Justice, Washington, D.C., for Respondent.

PUBLISHED REMAND DECISION DENYING ENTITLEMENT*

Walter Ray Graves and Lisa Graves, representatives of the estate of their daughter,
Hayley, claim that Prevnar, a pneumococcal vaccine, caused Hayley's death. The Graveses seek
compensation for Hayley's death, pursuant to the National Childhood Vaccine Injury Act, 42

* Because this published decision contains a reasoned explanation for the special master's
action in this case, the special master intends to post it on the United States Court of Federal
Claims's website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116
Stat. 2899, 2913 (Dec. 17, 2002).

All decisions of the special masters will be made available to the public unless they
contain trade secrets or commercial or financial information that is privileged and confidential, or
medical or similar information whose disclosure would clearly be an unwarranted invasion of
privacy. When such a decision or designated substantive order is filed, a party has 14 days to
identify and to move to delete such information before the document's disclosure. If the special
master, upon review, agrees that the identified material fits within the categories listed above, the
special master shall delete such material from public access. 42 U.S.C. § 300aa-(12)(d)(4);
Vaccine Rule 18(b).

U.S.C. §§ 300aa-1 et seq. (2006). An October 14, 2008 decision found that the Graveses failed to establish that Prevnar directly caused Hayley's seizures. The Graveses filed a motion for review with the United States Court of Federal Claims ("the Court"). Before adjudicating this motion, the Court remanded the case to resolve an alternate theory, that Prevnar significantly aggravated Hayley's pre-existing seizures so that they became more intense and uncontrollable, leading to her death. Order, filed April 9, 2009.

In accord with the remand order, the parties filed supplemental expert reports and another hearing was held. The Graveses have failed to establish, by a preponderance of the evidence, that Prevnar can affect the nervous system. The evidence upon which the Graveses and their experts rely is based upon studies in which the putative active agent, a substance called interleukin 1 β , was administered to rodents in doses far exceeding what Hayley experienced. Thus, the Graveses have failed to establish that they are entitled to compensation for their daughter's untimely death.

I. Factual History

The previous decision describes Hayley's unfortunate medical history. Medical records created contemporaneously with the events being described present the following facts, which are not disputed.

Hayley was born on November 4, 1999. Exhibit 14. When she was four months, her pediatrician recommended physical therapy because Hayley could not move her head to the left. At nine months, Hayley's pediatrician said her gross motor development was delayed and, again, recommended physical therapy. Exhibit 1 at 16, 31.

During this nine-month appointment with her pediatrician, which occurred on August 8, 2000, Hayley received the second dose of Prevnar. Exhibit 1 at 29, 31, 33. The Graveses seek compensation for Prevnar's alleged effects on Hayley.

On August 10, 2000, Hayley had a left arm and leg focal seizure. During the seizure, Hayley remained alert and drank some formula from her bottle. The Graveses brought Hayley to Cook Children's Medical Center emergency room, where she received anti-seizure medication. Exhibit 2 at 1, 5.

In the Cook County Pediatric Intensive Care Unit, Hayley was evaluated by Dr. Brian Ryals, a pediatric neurologist, for her seizures. To control her seizures, she received more medication and an EEG continuously monitored Hayley. Exhibit 2 at 14. Dr. Ryals noted that Hayley's family was concerned that her vaccinations may have caused her seizures. However, Dr. Ryals did not express an opinion as to whether the vaccinations were the cause of Hayley's injuries. The Graveses wanted Hayley evaluated for epilepsy and Dr. Ryals concurred. Exhibit 2 at 3.

Consequently, on August 29, 2000, Hayley was transferred from Cook County Medical Center to Hermann Hospital. Although Hermann Hospital has an epilepsy center, Hayley was admitted to the pediatric intensive care unit. Hayley remained at Hermann Hospital until she died on September 24, 2000. Exhibit 10B at 119.

The details of her nearly one-month stay in Hermann Hospital, as noted in the October 14, 2008 decision, are generally not relevant to determining whether Prevnar caused Hayley's seizures to last longer than the seizures would have lasted in the absence of the Prevnar.

Hayley's doctors attempted several different therapies to stop the seizures. These efforts, unfortunately, did not succeed.

II. Procedural History

The October 14, 2008 decision recounts the procedural history until that date. This history is summarized as follows.

The Graveses filed their petition in 2002 and filed medical records periodically. After a lapse of approximately four years, the Graveses filed reports from two doctors, Dr. Marcel Kinsbourne, a neurologist, and Dr. Vera Byers, an immunologist. Doctors Kinsbourne and Byers opined that Prevnar caused Hayley's seizures. Exhibit 15² & 17. Dr. Kinsbourne submitted a supplemental report, which was filed as exhibit 29. The Graveses' experts basically assert the theory that the Prevnar vaccine induced Hayley to produce interleukin-1 β (commonly abbreviated as IL-1 β) and that IL-1 β affected Hayley's neurological system.³

Respondent filed a report from Dr. Michael Kohrman, a neurologist. Exhibit C. Dr. Kohrman disagreed with the ultimate conclusions of Doctors Kinsbourne and Byers that Prevnar caused Hayley's seizures. Among the points of disagreement between Dr. Kohrman and the Graveses' experts was whether some studies on which Dr. Byers relied showed that Prevnar can cause seizures in the absence of a fever. Exhibit C at 5-6.

² Dr. Kinsbourne stated that Prevnar "is the most likely to have caused the onset of the epilepsy that ultimately caused Hayley's death." Exhibit 15 at 4.

³ Interleukin 1B is a cytokine. Tr. 120. Cytokines are messengers that communicate between cells in the immune system. Tr. 198; see also Dorland's Illustrated Medical Dictionary (30th ed. 2003) at 469.

The experts explained their competing views during a hearing, which was held over the course of three sessions. One topic of testimony was the dose of IL-1 β used in various studies on which Dr. Byers relied. In a supplemental report filed in response to Dr. Byers's testimony, Dr. Kohrman noted that the 1999 Vezzani article (exhibit 28) (Annamaria Vezzani, Interleukin-1 β Immunoreactivity and Microglia Are Enhanced in the Rat Hippocampus by Focal Kainate Application: Functional Evidence for Enhancement of Electrographic Seizures, 19(12) J. of Neuroscience 5024 (1999)) "demonstrated a dose dependent effect of the injection of IL-1B prior to injection of the convulsant agent kainic acid." Exhibit M at 3. In regard to Dubé, exhibit 23, Dr. Kohrman stated that the amount of IL-1 β used to produce a seizure was a dose that "is 10 times that necessary to modify other forms of seizures and this extremely high dose of IL-1B has not been demonstrated to be physiologically relevant." Id. at 4. Dr. Kohrman also stated that Hayley could not have produced enough IL-1 β to trigger a seizure. Id. at 5. Dr. Kohrman subsequently testified about the dose-dependent nature of IL-1 β and the amount of IL-1 β that Hayley could have produced in response to Pevnar. Tr. 195; tr. 201-05; tr. 207-09; tr. 248-52. In rebuttal, Dr. Byers agreed that the effect of IL-1 β varies by dose. Tr. 340.

At the end of the hearing, the parties declined the opportunity to file briefs. A decision was issued on October 14, 2008, denying the Graveses compensation. The decision was based upon various reasons, including a finding that the Dubé study was not analogous to Hayley's case because the mice in the Dubé study received a "high dose" of IL-1 β . Decision, slip op. at 24, 2008 WL 4763730, at *13 (quoting exhibit 23 (Dubé) at 154). Ultimately, the decision found that the Graveses had failed to establish, by a preponderance of the evidence, the reliability of

their theory that Prevnar can cause seizures in the absence of fever. Decision, slip op. at 27, 2008 WL 4763730, at *15.

After the decision was issued, the Graveses filed a motion for review with the Court. The Court has not ruled upon this motion. Instead, the Court remanded and ordered a “supplementary decision addressing whether the intractable nature of Hayley’s seizures and/or their duration comprised a substantial factor in bringing about Hayley’s death and, if so, whether the reaction to Prevnar vaccine in Hayley’s system, was a substantial causal factor with respect to the intractability and/or duration of the seizures she suffered.” Order, filed April 9, 2009.

The parties took steps to comply with the Court’s instructions on remand. Initially, the parties filed supplemental reports from their experts and associated literature. Concurrently, the Court also authorized a re-examination of the October 14, 2008 decision based upon the Federal Circuit’s decision in Andreu v. Sec’y of Health & Human Servs., 569 F.3d 1367 (Fed. Cir. 2009), which had been issued a few days earlier. Order, filed June 26, 2009.

The parties filed memoranda addressing Andreu and supplemental reports from their experts. In his reports leading to the February 19, 2010 hearing, Dr. Kohrman stated that the dose of IL-1 β was a crucial issue. Exhibit O (stating “Key to understanding the experimental studies by Vezzani is that in the animal model discussed IL-1b is not given as a systemic dose. Instead IL-1b is injected directly in the hippocampus of rats. * * * In these rats preinjected with IL-1b prior to inducing seizures with kainic acid, the concentration of IL-1b injected was 10 (-9th) molar. . . One tenth of this dose did not prolong the seizures or change the number of seizures or time to onset of seizures in Vezzani’s experiment.”).

Another hearing was held. Doctors Byers and Kinsbourne testified for the Graveses and Dr. Kohrman testified for respondent. Dr. Byers' testimony provided the foundation for Court Trial Exhibit 1. Tr. 519. Court Trial Exhibit 1 compared the amount of IL-1 β in different situations. As discussed below, the experts testified extensively about the effects of IL-1 β at different doses.

After this session of the hearing, the parties wished to file briefs, which they have done. Upon review of the briefs and transcript, one additional article (the 2000 Vezzani article) was ordered to be filed into the record. Each party presented one expert report addressing this article. The evidentiary submissions are complete and the case is ready for adjudication.

III. Standards for Adjudication

Petitioners who seek compensation for injuries not listed on the Vaccine Injury Table may pursue two alternatives: either a cause of action that a vaccine initially caused their injury or a cause of action that a vaccine significantly aggravated an underlying condition. 42 U.S.C. § 300aa-11(c)(1)(C)(ii)(I). For these causes of action, some elements overlap. Elements that are common to a causation-in-fact theory and a significant aggravation theory include “a medical theory causally connecting the vaccination and the injury” and “a logical sequence of cause and effect showing that the vaccination was the reason for the injury.” See Althen v. Sec’y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005) (defining elements for a case in which petitioners alleged the vaccine caused an injury); Loving v. Sec’y of Health & Human Servs., 86 Fed. Cl. 135, 142 (2009) (defining elements for a case in which petitioners alleged the vaccine significantly aggravated an underlying condition and adopting the Althen test to the significant aggravation context).

For the elements that petitioners are required to prove, their burden of proof is a preponderance of the evidence. 42 U.S.C. § 300aa-13(a)(1). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. Moberly v. Sec’y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec’y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between “preponderant evidence” and “medical certainty” is important because a special master should not impose an evidentiary burden that is too high. Andreu, 569 F.3d at 1379-80 (reversing special master’s decision that petitioners were not entitled to compensation); see also Lampe v. Sec’y of Health & Human Servs., 219 F.3d 1357 (Fed. Cir. 2000); Hodges v. Sec’y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge’s contention that the special master confused preponderance of the evidence with medical certainty).

The preceding paragraphs explain what a petitioner is required to establish and what level of proof satisfies a petitioner’s obligation. The remaining issue is how to evaluate evidence submitted to meet the standard of proof on those elements.

A particular topic on which the Federal Circuit has guided special masters is the process for evaluating the testimony of expert witnesses. In the Vaccine Program, an expert’s opinion may be evaluated according to the factors identified by the United States Supreme Court in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 593-94 (1993). Terran ex rel. Terran v. Sec’y of Health & Human Servs., 195 F.3d 1301, 1316 (Fed. Cir. 1999). As recognized in Terran, the Daubert factors for analyzing the reliability of testimony are:

(1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and, (4) whether the theory or technique enjoys general acceptance within a relevant scientific community.

Terran, 195 F.3d at 1316 n.2, citing Daubert, 509 U.S. at 592-95.

The reliability of the expert's theory is not presumed. A "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." Moberly, 592 F.3d at 1324. Furthermore, the reliability of an expert's theory affects the persuasiveness of the evidence. Special masters may "inquir[e] into the reliability of testimony from expert witnesses. Weighing the persuasiveness of particular evidence often requires a finder of fact to assess the reliability of testimony, including expert testimony, and we have made clear that the special masters have that responsibility in Vaccine Act cases." Id. at 1325. The finding that an expert's opinion passes a minimal standard of reliability does not require acceptance of that expert's theory because "disputes about the degree of relevance or accuracy (above this minimum threshold [of reliability]) may go to the testimony's weight." i4i Ltd. Partnership v. Microsoft Corp., 598 F.3d 831, 852 (Fed. Cir. 2010).

In evaluating expert testimony and scientific literature, special masters should analyze scientific literature "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." Andreu, 569 F.3d at 1379. "In other words, a finding of causation in the medical community may require a much higher level of certainty than that required by the Vaccine Act to establish a prima facie case. The special master must take these differences into account when reviewing the scientific evidence."

Broekelschen v. Sec’y of Health & Human Servs., 89 Fed. Cl. 336, 343 (Fed. Cl. 2009), aff’d, No. 2009-5132, 2010 WL 3516444 (Fed. Cir. Sep. 10, 2010).

IV. Analysis

The Court’s orders broadly raise two topics. The April 9, 2009 order, which is the primary focus of the remand, requires a determination of whether Prevnar made Hayley’s seizures worse, even though the Prevnar vaccine did not cause the seizures. Fundamentally, the Court’s April 9, 2009 order is premised on the legal theory that Prevnar significantly aggravated Hayley’s underlying condition which was causing her seizures.

The second topic within the scope of the remand is whether the Federal Circuit’s decision in Andreu affects, if at all, the October 14, 2008 decision. This decision found that the Graveses had failed to establish, by a preponderance of the evidence, that Prevnar caused Hayley’s seizures.

A. Significant Aggravation

The Court’s April 9, 2009 order asks two questions: (1) did the intractability of Hayley’s seizures cause Hayley’s death, and, if so, (2) did Prevnar cause Hayley’s seizures to become intractable? The answer to the first question is clear because the extended duration of Hayley’s seizures caused her death. Exhibit 4 (death certificate). Respondent agrees with this conclusion. Resp’t Br., filed June 7, 2010, at 3 (citing exhibit P (Dr. Kohrman’s rebuttal expert opinion) at 1); accord tr. 548 (testimony of Dr. Kohrman). The affirmative answer to the Court’s first question means that second question must be addressed.

The answer to the second question is less clear, as the evidence is in conflict. The experts do not agree whether Prevnar contributed to the intractability and/or duration of Hayley’s seizures. The Graveses rely primarily upon the opinion of Dr. Byers and also find support in the

opinion of Dr. Kinsbourne. To show how Prevnar contributed to the intractability and/or duration of Hayley's seizures, the Graveses advance a theory with two parts. First, the Prevnar vaccine induces a recipient to produce IL-1 β .⁴ Second, IL-1 β can extend the duration of or intensify seizures.⁵ The Graveses assert that this is what happened to Hayley. See Pet'r Br., filed May 6, 2010, at 6-16 (citing Dr. Byers's testimony). For the reasons explained below, the Graveses have failed to connect what is reliably known about IL-1 β to what happened to Hayley.

1. Effects of IL-1 β

The Graveses begin by asserting that Prevnar induces a recipient to produce some amount of IL-1 β . This proposition is true on a more-likely-than-not standard. Tr. 442-43 (testimony of Dr. Byers).⁶ Finding that some IL-1 β is produced does not end the inquiry. The ensuing question, which is very important in evaluating the Graveses' claim, is whether a recipient of Prevnar could have produced a dangerous amount of IL-1 β .

Different amounts (or dose) of a drug have different effects. The dose-dependent nature of pharmaceuticals has been recognized in many cases, including cases in the Vaccine Program. For example, the decisions that found that the petitioners had failed to establish that vaccines caused autism discussed how different amounts of thimerosal caused different effects. Cedillo v.

⁴ As discussed in the October 14, 2008 decision, Dr. Byers assumed that Hayley continuously produced IL-1 β . Decision, slip op. at 18, 2008 WL 4763730 at*10; id., slip op. at 27-28, 2008 WL 4763730 at *15 (citing tr. 100-01, tr. 338, and tr. 352). This assumption may not be correct because some evidence shows that the amount of IL-1 β after a seizure falls after 24 hours. Exhibit 28 (Vezzani, Interleukin-1 β Immunoreactivity, (1999)) at 5060; tr. 540 (Dr. Kohrman, discussing this article); tr. 559 (same); tr. 581 (same). Dr. Byers agreed. Tr. 631.

⁵ The October 18, 2008 decision found that the Graveses had not established that IL-1 β can cause seizures. This decision is the subject of the pending motion for review.

⁶ Respondent seems to question this conclusion. Resp't Br. at 10-11.

Sec’y of Health & Human Servs., No. 98-916V, 2009 WL 331968, at *17 (Fed. Cl. Spec. Mstr. 2009), motion for review denied, 89 Fed. Cl. 158 (2009), aff’d, 2010 WL 3377235 (Fed. Cir. Aug. 27, 2010); Snyder ex rel. Snyder v. Sec’y of Health & Human Servs., No. 01-162V, 2009 WL 332044, at *147 (Fed. Cl. Spec. Mstr. Feb 12, 2009), motion for review denied., 88 Fed. Cl. 706 (2009); King ex rel. King v. Sec’y of Health & Human Servs., No. 03-584, 2010 WL 892296, at *6-8 (Fed. Cl. Spec. Mstr. March 12, 2010). This principle has been recognized in decisions by circuit courts of appeal.⁷ E.g. McClain v. Metabolife Intern., Inc., 401 F.3d 1233, 1242 (11th Cir. 2005) (finding that district court abused its discretion in admitting expert testimony when the expert did not provide opinions about the dose-response level for a drug that was alleged to have injured plaintiffs); Wright v. Willamette Industries, Inc., 91 F.3d 1105, 1106 (8th Cir. 1996) (applying Arkansas law, stating “a plaintiff in a toxic tort case must prove the levels of exposure that are hazardous to human beings generally as well as the plaintiff’s actual level of exposure,” and reversing jury’s verdict).

Consistent with the scientific principles recognized in those cases, the evidence in this case showed that all exposures to IL-1 β are not hazardous. The effect of IL-1 β varies by amount. Dr. Byers testified that in animal models, some doses of IL-1 β do produce a seizure and some doses of IL-1 β do not produce a seizure. Tr. 487-89; tr. 493. Dr. Kohrman’s general opinion was that IL-1 β has been shown to extend the duration of seizures only when IL-1 β was given at high doses. Exhibit M at 3 (discussing exhibit 28 (Vezzani 1999)). In contrast, at low levels, IL-

⁷ Decisions by regional circuit courts of appeal have persuasive value because petitioners in the Vaccine Program, who seek compensation for off-Table injuries, are “treated as the equivalent of the tort plaintiff.” Walther v. Sec’y of Health & Human Servs., 485 F.3d 1146, 1151 (Fed. Cir. 2007).

1 β actually protects the nervous system. Tr. 543 (discussing exhibit 69 (Annamaria Vezzani, The Role of Cytokines in the Pathophysiology of Epilepsy, 22 *Brain, Behavior, and Immunity* 800 (2008)); tr. 553 (same); tr. 566; tr. 588.

The Graveses attempted to show that IL-1 β can lengthen the duration of a seizure at relatively low levels. The effects of low-level doses of IL-1 β were discussed at the February 19, 2010 hearing. In their brief filed after the hearing, the Graveses cited two articles (exhibit 69 and exhibit 70) and the associated testimony of Dr. Byers and Dr. Kinsbourne. Pet'r Br., filed May 6, 2010, at 12-14. Exhibit 70 (Teresa Ravizza, Innate and Adaptive Immunity during Epileptogenesis and Spontaneous Seizures: Evidence from Experimental Models and Human Temporal Lobe Epilepsy, 29 *Neurobiology of Disease* 142 (2008)) is far afield. Exhibit 70 discusses experiments done on people whose epilepsy is chronic. Tr. 591. Dr. Byers's interpretation of this article was that it showed that "IL-1 beta is produced by the inflammation and it causes additional inflammation." Tr. 450. Dr. Byers's testimony did not state that the Ravizza article indicated that the IL-1 β prolonged the seizures and did not discuss the dose of IL-1 β involved. Thus, Ravizza does not show that small doses of IL-1 β can prolong a seizure.

The other article cited by the Graveses in their brief was exhibit 69. On the surface, exhibit 69 offers some support for the opinions of Dr. Byers and Dr. Kinsbourne. "The preapplication of IL-1 β in rodent brain, by using concentrations within the range of those endogenously produced by seizures, prolongs the duration of seizures induced by intracerebral injection of chemoconvulsant drugs, such as the glutamate analog kainic acid or the GABA_A antagonist bicuculline." Exhibit 69 (Vezzani (2006)) at 799. The Graveses' experts commented upon this passage's use of the phrase "endogenous amounts." Tr. 443-48; tr. 469-70; tr. 593-94.

For the proposition that IL-1 β was given in endogenous amounts, the authors cited two earlier studies by Vezzani, one published in 1999 and the other published in 2000. The 1999 Vezzani paper had been filed into the record as exhibit 28. The experts discussed the 1999 Vezzani paper in the hearings held before the initial decision, tr.113; tr. 326-27; tr. 338-40; tr. 342-49 (Dr. Byers); tr. 195-99; tr. 247-49; tr. 390-92; tr. 394-98; tr. 415-16 (Dr. Kohrman); and in the hearing after the Court's remand. Tr. 471-75; tr. 480-82; tr. 486-87; tr. 510-11 (Dr. Byers); tr. 533; tr. 538; tr. 540; tr. 560; tr. 581-84; tr. 587-88 (Dr. Kohrman); tr. 630-31 (Dr. Kinsbourne). The information provided by Dr. Byers indicates that the amount of IL-1 β given in the experiment reported in the 1999 Vezzani paper exceeded greatly the amount of IL-1 β that is produced endogenously. See Court Exhibit 1; tr. 519-22.⁸

Consequently, the assertion in the 2006 Vezzani paper about endogenous amounts of IL-1 β was supported, if at all, by the 2000 Vezzani paper. See tr. 587-88. Because of the importance of this reference and because the 2000 Vezzani paper was not in the record at the time of the hearing, a July 1, 2010 order required that petitioners place the 2000 Vezzani paper into the record and also afforded both parties an opportunity to comment on that article. The

⁸ When Dr. Kohrman attempted to quantify the magnitude of the difference between the amount of IL-1 β used in experiments with animals and the amount of IL-1 β that could be produced by a person in response to Prevnar, Dr. Kohrman made math errors. See tr. 522-24; exhibit S at 2-3. Citing these math errors and other alleged deficiencies, the Graveses argue that "this Court cannot assign any credibility to the testimony of Dr. Kohrman." Pet'r Reply at 2; accord Pet'r Br. at 17-19.

The Graveses' arguments to detract from Dr. Kohrman's persuasiveness are misdirected in the sense that the Graveses are required to show, by a preponderance of the evidence, the reliability and persuasiveness of their expert, Dr. Byers. Dr. Kohrman's errors do not necessarily make Dr. Byers correct. As discussed in the text, Dr. Byers's own interpretation of Vezzani 1999 and Vezzani 2000 support the finding that the amount of IL-1 β used in those experiments was much greater than the amount of IL-1 β that would be produced by a child who did not have a fever.

Graveses filed the 2000 Vezzani paper as exhibit 76 (Annamaria Vezzani, Powerful Anticonvulsant Action of IL-1 Receptor Antagonist on Intracerebral Injection and Astrocytic Overexpression in Mice, 97(21) Proc. of the Nat'l Acad. Of Sciences of U.S. 11534 (2000)) and a report by Dr. Byers as exhibit 77. Respondent filed a report by Dr. Kohrman as exhibit U.

As explained by Dr. Byers, the experiment described in the 2000 Vezzani paper did not use endogenously produced amounts of IL-1 β . Dr. Byers concluded that “the smallest amount of endogenous IL-1 β which results from bicuculline induced seizures is between 1.02 and 10.2 ng.”⁹ Exhibit 77 at 2. (The abbreviation ng stands for nanogram.) Dr. Byers also stated that in the experiment reported in the 2000 Vezzani paper, “The amount of IL-1 β used to worsen the seizures was 51 ng.” Id. at 1. Thus, according to Dr. Byers’s calculations, the amount of IL-1 β used in the experiments was at least five times greater than the amount of endogenously produced IL-1 β (51 ng compared to 10.2 ng) and could be as much as 50 times greater (51 ng compared to 1.02 ng). The mean is approximately nine times greater (51ng compared to the average of 1.2 ng and 10.2 ng). It is important to emphasize that Dr. Byers’s materials support the finding that the 2000 Vezzani article used very high doses of IL-1 β .

A finding that the researchers did not use an endogenous dose of IL-1 β in either the experiment reported by the 1999 Vezzani paper or the experiment reported by the 2000 Vezzani paper contradicts the assertion in the 2006 Vezzani paper. As stated previously, the 2006 Vezzani paper asserted that “The preapplication of IL-1 β in rodent brains, by using concentrations within the range of those endogenously produced by seizures, prolongs the duration of seizures” induced by other means. Exhibit 69 at 799. The underlying data (Vezzani

⁹ How Dr. Byers reached this conclusion is not clear.

1999 and Vezzani 2000) do not support this summary.¹⁰ Therefore, a preponderance of the evidence shows that IL-1 β given to mice extends the duration of a seizure, which was provoked by other means, at doses that exceed the amount produced by mice normally.

The finding that IL-1 β extends the duration of seizures at relatively high levels is consistent with how IL-1 β affects fevers. (Fever can be seen as a step between a normal condition and a seizure.) A fever-producing substance is known as a pyrogen. Dorland's Illustrated Medical Dictionary (30th ed. 2003) at 1554. IL-1 β is a pyrogen. Tr. 466 (Dr. Byers). Thus, a logical expectation is that IL-1 β will cause a fever before it does anything worse. This progression of problems has been seen in animal models. Tr. 529-31 (discussing exhibit 23 (Dubé)).

As to whether some quantity of IL-1 β would trigger a fever before the IL-1 β would extend or provoke a seizure, Dr. Byers stated that a fever would not be necessary. Tr. 357; tr. 363; tr. 501. However, Dr. Byers's position is not persuasive because it fails to account for the fact that IL-1 β is a pyrogen, a fever-producing substance.

In sum, the evidence shows the following about what IL-1 β does. At small levels, IL-1 β appears to have a beneficial effect. At an increased level, IL-1 β appears to have no effect. At still higher levels, IL-1 β may induce a fever. At very high levels, IL-1 β may extend the duration of a seizure. This background information is useful in assessing the parties' arguments as to whether Hayley responded to Prevnar in a way that substantially contributed to her unfortunate death.

¹⁰ Even peer-reviewed medical articles may contain inaccuracies. See In re Rezulin Products Liability Litigation, 369 F. Supp. 2d 398, 423 n. 159 (S.D.N.Y. 2005) (citing cases).

2. Hayley's Response to Prevnar

Given the finding that different amounts of IL-1 β can produce different effects, the burden fell to the Graveses, as the petitioners, to present persuasive evidence to show that any amount of IL-1 β generated by Hayley in response to Prevnar was more likely to be an amount that was deleterious and not an amount that was beneficial.¹¹ To be consistent with the evidence about how IL-1 β affects living beings, the Graveses needed to establish, by a preponderance of the evidence, that Prevnar induced Hayley to produce a relatively large amount of IL-1 β . Such a showing would support “a logical sequence of cause and effect showing that the vaccination was the reason for the injury.” Althen, 418 F.3d at 1278.

A preponderance of the evidence establishes that Hayley produced an amount of IL-1 β in response to Prevnar that was far less than the amount capable of extending a seizure. Dr. Kohrman consistently and persuasively explained that if, as suggested by Dr. Byers's opinion, the Prevnar vaccine were causing IL-1 β to accumulate over the course of more than 40 hours, then Hayley should have displayed some symptoms, particularly a fever, before having her first seizure. Tr. 201-03; tr. 207; tr. 221-24 (“in physiologic doses, [cytokines] have not been shown to produce seizures in the absence of fever”); tr. 238-39; tr. 242-43; tr. 251-52; tr. 255; tr. 403-04; tr. 549-50. Hayley's clinical picture provides some indirect evidence of how much IL-1 β she produced. A preponderance of the evidence supports a finding that Hayley did not have a fever after Prevnar. Tr. 24 (Mr. Graves); tr. 63 (Dr. Kinsbourne); tr. 201; tr. 221 (Dr. Kohrman). This

¹¹ The Graveses argue that such a burden would be akin to requiring “scientific certainty.” Pet'r Reply at 2. This argument is flawed because the Federal Circuit has recognized that requiring petitioners to establish their case by the preponderance of evidence is not the same as requiring scientific certainty. Moberly, 592 F.3d at 1322; Hodges, 9 F.3d at 962-63.

lack of fever necessarily places Hayley on a point in the dose-response curve where IL-1 β is at a level below the amount necessary to extend the duration of any seizure.

Relatively little evidence controverts Dr. Kohrman's logic. The Graveses' expert, Dr. Byers, stated that "I don't know how much IL-1 beta" was produced by Hayley. Tr. 489.¹² When Dr. Byers was questioned further about whether any tests have been conducted to determine the amount of IL-1 β induced by Pevnar in any children,¹³ Dr. Byers indicated that these tests had been done but she could not identify any articles about Pevnar. Tr. 491.¹⁴

Dr. Byers's lack of information about how much IL-1 β a person produces in response to Pevnar leaves a gap in the Graveses' case.¹⁵ Dr. Kohrman supplied a logical and persuasive analysis of Hayley's condition. Because there is no evidence that Hayley had a fever, Hayley's production of IL-1 β was less than the amount of IL-1 β needed to extend the duration of any seizure.

¹² Dr. Kinsbourne also did not provide any information about the amount of IL-1 β that Hayley could have produced in response to Pevnar. Tr. 606.

¹³ The reliability of an expert's opinion may be evaluated by considering whether the theory has been tested. Daubert, 509 U.S. at 593.

¹⁴ Dr. Byers discussed exhibit 39 (Peter J.G. Zwijnenberg et al., IL-1 Receptor Type 1 Gene-Deficient Mice Demonstrate an Impaired Host Defense Against Pneumococcal Meningitis, 170 The Journal of Immunology 4724-30 (2003)). The Zwijnenberg article offers little help in the task of trying to estimate how much IL-1 β a person such as Hayley produces in response to Pevnar because Zwijnenberg studied how mice responded to *S. pneumoniae*, which is one of the infectious organisms to which Pevnar is directed. Exhibit 39 at 4725; accord tr. 491-92 (Dr. Byers discussing this article). Zwijnenberg did not study how mice responded to Pevnar or to IL-1 β , which is the specific question at issue here.

¹⁵ Dr. Byers was not required to "know" with scientific certainty the amount of IL-1 β that a child like Hayley would have produced. See Andreu, 569 F.3d at 1380; Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994).

Ultimately, the Graveses have failed to show, by a preponderance of the evidence, that Plevnar induced the production of an amount of IL-1 β that could have lengthened Hayley's seizures. A preponderance of the evidence shows that IL-1 β can affect the duration of seizures only when the amount of IL-1 β exceeds what is produced endogenously. Thus, any (small) amount of IL-1 β that Hayley produced in response to Plevnar was not sufficient to extend the duration of Hayley's seizures. See tr. 624. Therefore, the answer to the Court's question, which asked "whether the reaction to Plevnar vaccine in Hayley's system, was a substantial causal factor with respect to the intractability and/or duration of the seizures she suffered," is "no."

B. Initial Causation as Discussed in the October 14, 2008 Decision

The remand from the Court also permitted reconsideration of the October 14, 2008 decision because of an intervening precedent from the Federal Circuit, Andreu. Order, filed June 26, 2009. After the June 26, 2009 order, the Federal Circuit has issued other decisions about the Vaccine Program. These decisions do not affect the resolution of the Graveses' theory that the Plevnar vaccine was the initial cause for Hayley's seizures.

The Graveses argued that Andreu favored a finding of compensation. They presented three arguments for why the October 14, 2008 decision was flawed (1) it created a new rule for evaluating testimony given by treating physicians; (2) it burdened the Graveses with the obligation to support the opinion of the experts with medical literature; and (3) it looked at Hayley's clinical picture. Pet'r Br., filed July 27, 2009. These arguments are not persuasive.

First, the October 14, 2008 decision's evaluation of the testimony of treating doctors is consistent with Andreu. The October 14, 2008 decision found that the testimony of Dr. Wheless was not persuasive because the underlying article on which Dr. Wheless relied, the Wise article,

did not support Dr. Wheless’s opinion that Prevnar can cause seizures in the absence of fevers. Decision, slip op. at 11, 2008 WL 4763730, at *8.¹⁶ Although the Graveses argue that the “special master did not afford the appropriate weight to Dr. Wheless’ testimony,” Pet’r Br., filed July 27, 2009, at 3; the weighing of testimony has long been a function of special masters. Hodges, 9 F.3d at 967 (stating that “the factfinder must decide the reliability, consistency, and probative value of the scientific evidence, with guidance of scientific opinion.”). Andreu did not change this division of responsibilities. Moberly, 592 F.3d at 1325 (stating “Weighing the persuasiveness of particular evidence often requires a finder of fact to assess the reliability of testimony, including expert testimony, and we have made clear that the special masters have that responsibility in Vaccine Act cases.”) .

Second, the October 14, 2008 decision’s citation to medical literature is appropriate. “Although a Vaccine Act claimant is not required to present proof of causation to the level of scientific certainty, the special master is entitled to require some indicia of reliability to support the assertion of the expert witness.” Moberly, 592 F.3d at 1324.

Third, the Graveses argue that Andreu “criticized the special master’s requirement of a ‘clinical picture.’ [Andreu, 569 F.3d at 1381-82.] The special master in this case also created a ‘clinical picture’ requirement.” Pet’r Br., filed July 27, 2009, at 5. The Graveses overstate the holding in Andreu.

Before Andreu, petitioners were required to establish, by a preponderance of evidence, “a logical sequence of cause and effect showing that the vaccination was the reason for the injury;

¹⁶ Another special master found that this same Wise article did not establish a causal relationship between Prevnar and a seizure. Nance v. Sec’y of Health & Human Servs., No. 06-730V, 2010 WL 3291896, at *9 (Fed. Cl. Spec. Mstr. July 30, 2010).

and . . . a showing of a proximate temporal relationship between vaccination and injury.” Althen, 418 F.3d at 1278. The “logical sequence of cause and effect” requires some evidence that the vaccinee responded in a way that is in accord with the theory advanced by petitioners. If the vaccinee responded differently from how the petitioners’ theory predicts, then the proof would not be “logical.” See Lampe, 219 F.3d at 1367 (discussing expert testimony that the vaccinee did not respond in a way consistent with an adverse reaction to the vaccine). Similarly, the temporal relationship element also requires examining how the vaccinee’s injury became manifest. For example, if petitioners’ theory suggests that the minimal amount of time for a vaccine to cause damage is 10 days and the vaccinee shows sign of an injury 11 hours after vaccination, then the petitioners would not satisfy the third prong from Althen. Bazan v. Sec’y of Health & Human Servs., 539 F.3d 1347, 1352-53 (Fed. Cir. 2008). Thus, Andreu did not bar special masters from examining the clinical picture of the vaccinee as a matter of law.

In Andreu, the Federal Circuit discussed how an injury caused by a vaccine would appear. Based upon the testimony of the government’s expert, Dr. Herskowitz, the Federal Circuit found that the pertussis vaccine can cause ““a smaller amount of brain injury in a smaller area of the brain.”” Andreu, 569 F.3d at 1381. The Federal Circuit’s reliance on expert testimony suggests that the clinical expectation largely turns on the evidence. See also Althen, 418 F.3d at 1281 (stating that special masters decide on a case-by-case basis).

Compared to Andreu, the record in this case is much different. Dr. Kohrman was quite clear in stating that IL-1 β will cause a fever before it causes a seizure at least when IL-1 β is not given in a dose that exceeds the amount produced by the body normally. This escalation of problems distinguishes IL-1 β from the whole cell pertussis vaccine, as discussed by the Federal

Circuit in Andreu, 569 F.3d at 1381.¹⁷ Because of the difference in facts, Andreu does not compel a change in outcome.

For these reasons, neither Andreu nor any other intervening Federal Circuit decision requires a different outcome on the Graveses' theory that Prevnar caused Hayley's seizure initially.¹⁸

V. Conclusion

The Court's April 9, 2009 order directed the undersigned to consider whether Prevnar lengthened (or, in phrasing found in the Vaccine Act, significantly aggravated) Hayley's seizures. A preponderance of evidence does not support this theory.

The Court's June 26, 2009 order authorized a re-examination of the October 14, 2008 decision that found that a preponderance of evidence had not established that Prevnar caused Hayley's seizures initially. The intervening Federal Circuit precedents have not changed this analysis.

¹⁷ Similarly distinguishable is an article by Lee and Ong (exhibit 52 (Wei-Ling Lee and Hian-Tat Ong, Afebrile Seizures Associated with Minor Infections: Comparison with Febrile Seizures and Unprovoked Seizures, 31(3) *Pediatric Neurology* 157 (2004)), which the Graveses cited in one of their briefs after remand. Pet'r Second Memorandum, filed July 27, 2009, at 5. Lee and Ong discussed whether infections could cause seizures in the absence of a fever. This general information is less persuasive than the specific information about IL-1 β , which shows that fevers arise before seizures. See also Nance, 2010 WL 3291896, at *10.

¹⁸ Evidence that was filed during the remand reinforces one conclusion on a disputed point. Before the October 18, 2008 decision, Dr. Byers maintained that the IL-1 β caused the seizures in the Vezzani studies. Decision, slip op. at 21, 2008 WL 4763730, at *11 (citing tr. 115). However, in her most recent submission, Dr. Byers stated that IL-1 β "prolongs kainic acid/bicuculline induced seizures." Exhibit 77 at 2. A statement that kainic acid induced the seizures appears to be the equivalent of saying that IL-1 β did not cause the seizures. This was a finding in the October 18, 2008 decision.

Consequently, the Graveses are not entitled to compensation. Pursuant to Vaccine Rule 28.1(a), the Clerk's Office is instructed to deliver a copy of this decision to the assigned judge.

IT IS SO ORDERED.

S/ Christian J. Moran

Christian J. Moran
Special Master