In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

AMY N. HEDDENS,	*	
	*	No. 15-734V
Petitioner,	*	Special Master Christian J. Moran
	*	
v.	*	
	*	Filed: October 5, 2018
SECRETARY OF HEALTH	*	
AND HUMAN SERVICES,	*	Entitlement, HPV vaccine,
	*	multiple sclerosis, bench ruling
Respondent.	*	

Ronald C. Homer & Meredith Daniels, Conway & Homer, P.C., Boston, MA, for petitioner; Christine Becer, United States Dep't of Justice, Washington, DC, for respondent.

PUBLISHED DECISION DENYING COMPENSATION[1]

A hearing was held on October 1, 2018. After the parties submitted all their evidence, the undersigned issued a bench decision, finding that Ms. Heddens had failed to establish that she was entitled to compensation. See Doe/17 v. Sec'y of Health & Human Servs., 84 Fed. Cl. 691, 704 n. 18 (2008) (noting "[e]ven a special master's ruling on entitlement may be delivered from the bench, with no written opinion").

The undersigned is issuing this document for two reasons. First, if only a bench decision was issued, the public would not have access to the transcript containing the bench decision and, thereby, the reasoning underlying the decision. To allow public access to the reasoning underlying the decision, this document will become available to the public pursuant to 42 U.S.C. § 300aa-12(d)(4).

Second, this document provides an abbreviated recitation for the basis of decision. See Hebern v. United States, 54 Fed. Cl. 548 (2002) (example of a judge from the United States Court of Federal Claims formalizing a bench ruling denying a motion for review). As explained in the bench ruling, the undersigned considered all the evidence, including the medical records,

[1] The E-Government Act, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services), requires that the Court post this decision on its website. This posting means that the decision will be available to anyone with the internet. Pursuant to Vaccine Rule 18(b), the parties have 14 days to file a motion proposing redaction of medical information or other information described in 42 U.S.C. § 300aa-12(d)(4). Any redactions ordered by the special master will appear in the document posted on the website.

expert reports, medical articles, and oral testimony. The undersigned's consideration of this evidence began when the evidence was received. See Vaccine Rule 5.

The evidence shows that relatively few events in Ms. Heddens's medical record hold significance for determining whether she is entitled to compensation. On June 30, 2010, she went to a clinic for a "well woman exam," during which she reported frequent urination, loss of balance, and blurry vision when she moved her head. She also reported diarrhea and nausea. Exhibit 5 at 8. The expert whom the Secretary retained, Dr. Sriram, opined that this episode was an initial manifestation of multiple sclerosis ("MS"). Exhibit M at 2. In contrast, the expert whom Ms. Heddens retained, Dr. Napoli, disagreed. Exhibit 29 at 2. The person who conducted the June 30, 2010 examination, a physician's assistant named Cindy Shuman, seemed not to attribute any significance to these problems as Ms. Shuman did not suggest any follow up. See exhibit 5 at 10.

The next significant event in Ms. Heddens's medical history was her receipt of the third dose of the HPV vaccine on December 3, 2012. Between June 30, 2010 and December 2, 2012, Ms. Heddens did not report having any problems that the experts considered related to multiple sclerosis. Ms. Heddens alleges that the December 3, 2012 HPV vaccination harmed her.[2]

On January 18, 2013, Ms. Heddens experienced double vision and dizziness for which she sought treatment at an urgent care facility. She was referred to an emergency room. Exhibit 9 at 3. The emergency room doctor, in turn, referred her to an ophthalmologist. Exhibit 3 at 5-6. The ophthalmologist ordered an MRI. Exhibit 10 at 2.

The MRI was conducted on January 29, 2013. It showed multiple enhancing lesions. Exhibit 3 at 64-65.

When a neurologist, Dr. Ramirez, reviewed the results of the MRI, he diagnosed Ms. Heddens as suffering from MS. Exhibit 4 at 1-4.[3] Both Dr. Napoli and Dr. Sriram agree with the diagnosis of multiple sclerosis, although they, as mentioned earlier, differ as to whether Ms. Heddens's first clinical manifestation of MS was in June 2010 or January 2013. After Dr. Ramirez's diagnosis in 2013, Ms. Heddens has received medical care periodically. None of her treating doctors suggested that the HPV vaccination harmed Ms. Heddens. See Pet'r's Br. at 46-48; Resp't's Br. at 13. Otherwise, the details of the course of Ms. Heddens's MS are not relevant to determining whether the December 3, 2012 HPV vaccination harmed Ms. Heddens.

The analysis begins with a preliminary, but ultimately insignificant, issue — whether Ms. Heddens's case should be analyzed either as a claim that the HPV vaccine caused her to suffer an initial onset of MS or as a claim that the HPV vaccine caused her to suffer an aggravation of pre-existing MS. The undisputed testimony from the experts indicate that Ms. Heddens, most likely,

[2] Initially, Ms. Heddens alleged that the HPV vaccination caused her to suffer multiple sclerosis. But, as part of her pre-hearing brief, Ms. Heddens presented the alternative claim that the HPV vaccination significantly aggravated pre-existing multiple sclerosis. Pet'r's Br. at 2, 25.

[3] During this initial consultation, Dr. Ramirez recorded: "She has not been sick or received immunization recently." Exhibit 4 at 1.

had lesions in her brain before the HPV vaccination on December 3, 2012. These lesions appeared on her January 29, 2013 MRI. After Dr. Sriram reviewed the images from this MRI, he wrote that Ms. Heddens had 10 T2 lesions and 9 active lesions. Exhibit U at 1. At the hearing, Dr. Napoli agreed with Dr. Sriram's observations. Further, Dr. Sriram reasoned that number, size, and location of the lesions suggested that at least some of the lesions had to exist before the December 3, 2012 vaccination. Exhibit U at 2-3. Dr. Napoli agreed with this conclusion. Dr. Napoli testified that if Ms. Heddens had undergone an MRI on December 2, 2012, the day before the vaccination, this hypothetical MRI would have probably shown lesions. Based upon the agreement between the experts, the undersigned finds that Ms. Heddens most likely had lesions in her brain before receiving the December 3, 2012 HPV vaccination. This finding is sufficient to serve as a predicate for analyzing Ms. Heddens's case as a claim for significant aggravation.[4]

As a significant aggravation case, Ms. Heddens must establish the elements set forth in Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009). Importantly, the last three elements of the Loving test correspond to the three elements of an initial causation claim set forth in Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005). This decision turns on the outcome of the fourth Loving factor, which is the first Althen factor, whether the HPV vaccination can cause an exacerbation of MS.

Ms. Heddens has failed to meet her burden of proof on this element. Beyond the opinion from Dr. Napoli, the evidence falls into two categories: epidemiological and experimental.

The Secretary introduced epidemiological studies to undermine Ms. Heddens's attempt to establish that the HPV vaccine can aggravate (or cause) MS. See Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008) ("The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the petitioner's evidence on a requisite element of the petitioner's case-in-chief"). Some epidemiological studies investigated the precise question in the case at bar: whether the HPV vaccine affects MS. One article was a meta-study of 11 underlying studies. Exhibit S.[5] Another article was a study of nearly four million women from Denmark and Sweden, countries where MS is most prevalent. Exhibit E.[6] A third article, which carried the least weight, analyzed VAERS data. Exhibit F.[7] Collectively,

---

[4] Categorizing Ms. Heddens's case as one involving significant aggravation does not depend on the June 30, 2010 episode. As discussed during the oral bench ruling, whether the June 30, 2010 episode represented an unrecognized manifestation of MS, as Dr. Sriram opined, or was entirely unrelated to MS, as Dr. Napoli opined, is a closer question. But, resolution of this close question does not affect the outcome of Ms. Heddens's case.

[5] Julie Mouchet et al., Human papillomavirus vaccine and demyelinating diseases — A systemic review and meta-analysis, 132 Pharmacological Research 108 (2018).

[6] Nikolai Madrid Scheller et al., Quadrivalent HPV Vaccination and Risk of Multiple Sclerosis and Other Demyelinating Diseases of the Central Nervous System, 313 J. Amer. Med. Ass'n 54 (2015).

[7] Paolo Pellegrino, No evidence of a link between multiple sclerosis and the vaccine against the human papillomavirus, 28 Eur. J. Epidemiol. 705 (2013).

these studies did not support Ms. Heddens's argument that the HPV vaccine can aggravate (or cause) MS.

Another set of epidemiological studies examined whether vaccines other than the HPV vaccine caused or worsened MS. Exhibits C[8] and I.[9] They also have not detected a statistically significant increase in multiple sclerosis after various vaccines. Because these studies are not about the HPV vaccine, they carry less evidentiary value than the epidemiology directly on point. But, to the extent these additional studies contribute to the analysis, they tend to show that vaccinations do not contribute to MS.

However, epidemiology does not conclusively establish that the HPV vaccine cannot cause MS. A petitioner can argue that if a 12th study were conducted or if a study involved five million women, then the results might detect something that has evaded detection so far. Thus, the finding that Ms. Heddens failed to meet her burden of proof regarding Loving prong 4 / Althen prong 1 does not rest exclusively on the epidemiology.

Ms. Heddens relies upon Dr. Napoli's opinion that molecular mimicry is a reliable explanation to connect the HPV vaccination to a worsening of MS. In the pre-trial conference, the Secretary acknowledged that molecular mimicry is a valid theory to explain why the flu vaccine can cause Guillain-Barré syndrome.

Nevertheless, a simple invocation of the term "molecular mimicry" does not carry a petitioner's burden of proof. As explained by the Court of Federal Claims, "Without any empirical evidence that the theory actually applies to the influenza vaccine and [the disease in question], the first prong of Althen would be rendered meaningless." Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 135 (2011), aff'd without opinion, 463 F. App'x 932 (Fed. Cir. 2012).

Ms. Heddens has failed to present "empirical evidence" to support Dr. Napoli's opinion that the HPV vaccine can aggravate (or cause) MS. At the hearing, Dr. Napoli identified two articles as the primary support for his opinion: an article by Wucherpfennig and Strominger and an article by Kanduc.[10] But, neither article is supportive.

Wucherpfennig and Strominger.[11] These researchers explored whether various foreign antigens (viruses and bacteria) could inspire the production of T cells that would react with

---

[8] Frank DeStefano et al., Vaccinations and Risk of Central Nervous System Demyelinating Diseases in Adults, 60 Arch. Neurol. 504 (2003).

[9] Christian Confavreux et al., Vaccinations and the Risk of Relapse in Multiple Sclerosis, 344 N. Eng. J. Medicine 319 (2001).

[10] Based, in part, on the parties' pre-hearing briefs, the undersigned had identified those articles as the main articles on which Ms. Heddens and Dr. Napoli were relying.

[11] Kai W. Wucherpfennig and Jack L. Strominger, Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein, 80(5) Cell 695 (1995).

myelin basic protein. As a first step, Wucherpfennig and Strominger consulted a database, looking to see whether the amino acid sequence resembled (or mimicked) an epitope of myelin basic protein. Exhibit 21, tab C at 696-97. This database query identified more than 600 antigens that had some homology. Of this group, the researchers selected certain proteins for further testing. Of this group, seven came from types of the human papillomavirus. As a second step, Wucherpfennig and Strominger then tested whether these homologous antigens caused an expansion in the number of T cells that were known to react with myelin basic protein. This test showed that some, but not all, of the homologous antigens produced a strong response. Id. at 698-99, table 1. For example, the herpes simplex virus produced relatively large numbers of T cells. However, and importantly for this case, the seven types of the human papillomavirus did not generate a strong response. In addition, a different table, table 2, showed some reactivity to a part of the human papillomavirus not found in the HPV vaccine.

Dr. Sriram presented this critique in a report. Exhibit O at 2. When Dr. Napoli was asked to comment during the hearing, he stated that this article shows that there is potentially cross-reactivity.

Kanduc.[12] Unlike the Wucherpfennig experiment, which tested the human papillomavirus, Kanduc tested a portion of the HPV vaccine. Kanduc identified more than 80 strings composed of seven amino acids, known as heptapeptides, from HPV16 that matched sequences of amino acids in the human proteome. Based upon the function of the protein, Kanduc proposed that cross-reactivity could cause various problems. Exhibit 23, tab A at 66. But, none of those problems resemble the problems that appear in MS.[13]

When Dr. Napoli was asked about the limitations of Kanduc, he also responded that Kanduc shows the HPV vaccination could maybe serve as a trigger for an autoimmune reaction. This is true. Cross-reactivity is possible in theory. But, Ms. Heddens has provided no reliable basis for elevating this potentiality to a probability.

Requiring Ms. Heddens to present some support for the theory she proposes is consistent with W.C. v. Sec'y of Health & Human Servs., 704 F.3d 1352, 1360 (Fed. Cir. 2013), in which the Federal Circuit stated that although molecular mimicry may be well-regarded in some contexts, the special master "correctly required additional evidence showing that molecular mimicry can cause the influenza vaccine to significantly aggravated multiple sclerosis." The Federal Circuit further examined the special master's finding that the Wucherpfennig article showed some peptides were cross-reactive but others were not, and concluded that the special master's weighing of this evidence was not arbitrary or capricious. Id. at 1360-61. The support a petitioner provides does not have to reach a level of reliability that the theory is scientifically certain. See LaLonde v. Sec'y of Health & Human Servs., 746 F.3d 1334, 1339 (Fed. Cir. 2014) ("simply identifying a 'plausible' theory of causation is insufficient for a petitioner to meet her

[12] Darja Kanduc, Quantifying the possible cross-reactivity risk of an HPV16 vaccine, 8 J Experimental Therapeutics and Oncology 65 (2009).

[13] Ms. Heddens elicited testimony that one homologous protein, GALC, contributes to the production of myelin. However, according to Kanduc, the consequences of deficiencies in GALC appear before an individual is six months old. See exhibit 23, tab A at 72-73.

burden of proof"). But, even at the more-likely-than-not level of proof, Ms. Heddens has not overcome this hurdle.

A persuasive showing that the HPV vaccine can worsen (or cause) MS is, as explained above, part of Ms. Heddens's case under either the Loving or Althen framework. She has failed to meet the required showing. Thus, regardless of whether her claim is one for significant aggravation (based upon the uncontroverted assertion that she most likely had lesions in her brain before the vaccination) or whether her claim is a new onset claim, she is not entitled to compensation.

The undersigned directs the Clerk's Office to enter judgment based upon the decision in this case if a motion for review is not filed. When the time for filing a motion for review (see Vaccine Rule 23) begins to run is for an appellate tribunal to decide.

IT IS SO ORDERED.

s/Christian J. Moran
Christian J. Moran
Special Master