CADTH

CADTH COMMON DRUG REVIEW

Patient Input

Onpattro (Patisiran)

(Alnylam Netherlands BV)

Indication: Polyneuropathy in hereditary transthyretin-mediated amyloidosis

CADTH received patient input from:
Canadian Organization for Rare Disorders with support of Canadian Amyloidosis Support Network

February 15, 2019

CADTH

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	Onpattro (Patisiran)
Name of the Patient Group	Canadian Organization for Rare Disorders with support of Canadian Amyloidosis Support Network
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
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1. About Your Patient Group

If you have not yet registered with CADTH, describe the purpose of your organization. Include a link to your website.

Canadian Organization For Rare Disorders (CORD)

CORD is Canada's national network for organizations representing all those with rare disorders. CORD provides a strong common voice to advocate for health policy and a healthcare system that works for those with rare disorders. CORD works with governments, researchers, clinicians and industry to promote research, diagnosis, treatment and services for all rare disorders in Canada.

https://www.raredisorders.ca/

The CASN is a not-for-profit, all volunteer organization, formed by amyloidosis patients and family members of amyloidosis patients. The CASN offers a toll-free helpline, an educational website, and a support community connected through social media and meetings.

http://thecasn.org/

2. Information Gathering

Recruitment: Participants were recruited through two patient networks for amyloidosis, of which the target patient population, hereditary amyloidosis transthyretin (hATTR), is a small subset. Both networks are patient-based, offering education and support through website and Facebook as well as in-person meetings. The US-based network, Amyloidosis Support Groups, Inc. has support groups in over 35 US cities as well as global patient engagement, including the Canadian Amyloidosis Support Network, Inc. (CASN) based in Toronto (Canada). The CASN is a not-for-profit, all volunteer organization, formed by amyloidosis patients and family members of amyloidosis patients. The CASN offers a toll-free helpline, an educational website, and a support community connected through social media and meetings.

Sadly, while there was one Canadian site that took part in the patisiran clinical trials, we were unable to directly recruit patients from that trial because the physician was not willing to contact the patients to inform them about the patient input submission and to obtain their agreement to take part. Despite several attempts to explain the legitimacy and importance of the input process, the physician believed it would be violation of patient confidentiality to contact them about something they "had not previously consented to receiving information about."

Responses: Patients provided input through individual interviews (3), written testimonials (5), and online survey (51). All those who provided individual interviews or testimonials also completed the online survey. While the survey link was distributed to all members of the amyloidosis groups, the instructions targeted patients and caregivers affected by hATTR.

Among the 51 respondents, 73% identified as a person diagnosed with hATTR and another 4% said they were not diagnosed with hATTR but had symptoms consistent with hATTR. Another 4% responded they had no diagnosis or were unsure as to their type of amyloidosis. Additionally, 10% identified as living with a type of amyloidosis similar to hATTR (for example, familial nephropathic systemic amyloidosis or nonfamilial wild-type ATTR). Finally, 10% of survey respondents identified as caregivers for someone with hATTR (spouse or child of).

Diagnosis: The respondents reflected a "typical" profile for hATTR patients. About half (53%) were diagnosed when they were between the ages of 60 and 79 years old, while slightly more than one-third (36%) were diagnosed between 40 and 59 years old. Less than 6% said they were between 20 and 39 years old when diagnosed and none were over the age of 80 when diagnosed.

In terms of time since diagnosis, almost half (47%) said it had been diagnosed for two to five years. Almost one-fifth (19%) said they had been diagnosed five to 10 years ago, while 14% said they had received their diagnosis between one and two years ago, and another 8% were relatively newly diagnosed less than one year ago.

Geographic location: The majority of the patients represented in the survey identified as males (70%) and 30% as females. Among those who specified a country of residence (38 respondents), 61% were in the USA, 37% in Canada, and one person elsewhere (Ireland). Among Canadian respondents, the majority (80%) reside in Ontario and the remainder in Alberta and BC.

3. Disease Experience

Interviewees and survey respondents were asked to describe in their own words the experience of living with or caring for someone with hATTR, as well as the impact on family and others. There is no doubt that hATTR is experienced as a seriously debilitating condition affecting multiple systems in the body resulting in significant physical damage, pain, and psychological distress. Moreover, the disease severely impacts daily functioning and quality of life not only for the individual but the whole family.

I have neuropathy of the arms and legs, it's affected my heart, and has caused gastro paralysis at times. My weight loss has been great and I have also had muscle deteriorated.

My extended family has lived with Familial Amyloidosis for several generations. I grew up watching it slowly kill my grandfather, great uncle and uncle. My mother was severely sick with it by the time I was a teenager. …. I grew up afraid for the adults in my family ,,,. When I found out I had it, I fell into a severe depression

It is quite debilitating, and each day it progresses, requiring changes and adaptation big and small to day to day living. It went from difficulty walking distances to not being able to walk at all in 4 years. All muscles in legs and arms are atrophied now, presenting giant mobility problems. Gastro issues, somewhat well controlled by tincture

of opium, still mean there are many times I can't leave the house for fear of diarrhea.

hATTR caused much suffering for my father and uncle. I have several siblings with the mutation. One brother with hATTR died during heart surgery on his 69th birthday. I have problems with heart, digestion, and peripheral neuropathy.

The survey also presented a list of physical effects of hATTR and respondents were asked to rate the degree to which they experienced difficulties or problems with each, on a five-point scale

identified as “no problem, never”, “minor, infrequent”, “moderate, sometimes”, “serious, frequent”, and “incapacitating, regularly.” The symptoms rated as most difficult were those

related to “nerve damage: tingling, numbness, burning pain, carpel tunnel, weakness” with more than one-third reporting the impact was “serious” or one-fifth as “incapacitating.” Only one- tenth reported no problems with neuropathy while the remaining one-third said the symptoms were “moderate.” Gastro-intestinal symptoms constituted the second most severe and frequently experienced impact. More than half (51%) said they had “serious, frequent” or “incapacitating, regular” difficulties with GI-related “sexual dysfunctions, sweating, dizziness upon standing, weight loss” while less than one-third (31%) said they had no or minor difficulties with these symptoms. Other GI symptoms, “such as diarrhea, nausea, constipation, urinary tract infections” were experienced to a slightly lesser degree although still “serious, frequent” or “incapacitating, regular” to over one-third of respondents.

Cardiac symptoms were somewhat less pronounced in this cohort with 40% reporting “serious, frequent” and “incapacitating, regular” difficulties with “palpitations, arrhythmia, and chest pain” and half indicating these were either nonexistent or minor difficulties. Similarly, nearly two-fifths said lesser cardiac symptoms of “leg swelling, fatigue, shortness of breath, dizziness” were minor or nonexistent problems, with one-third experiencing them as “moderate” and about one-fourth as “serious.

4. Experiences With Currently Available Treatments

Specific treatments: benefits, side effects and management: Until very recently, there were no specific therapies for the treatment of hATTR. Most patients have received treatment to manage symptoms related to organ damage, namely heart damage, nerve damage, and inflammation. About 75% of respondents reported having received, currently or in the past, treatment(s) related to hATTR, 15% had not, and about one-tenth said they were unsure as to whether they had received specific hATTR treatment

Survey respondents were presented with a list of treatments and asked to indicate whether they used in

the past, were using currently, or had used, with an option for “not sure.” Given that the liver is the site of TTR production, liver transplantation was once considered a routine or “standardized” curative or life- extending option, albeit not recommended or accessible to all hATTR patients (given the lack of available livers for transplant). However, longer-term evidence indicated that symptoms often reoccurred, albeit with several intervening years of quality health.

Only three respondents indicated receipt of a liver transplant; one of them resided in Canada and the other two were in the USA. The therapy reported as used by most respondents (64%), either currently or in the past, was Diflunisal, a nonsteroidal anti-inflammatory drug; additionally, one-third reported using at least one other drug to reduce inflammation. More than half had used or were currently taking some form of cardiac management therapy, specifically to manage blood pressure (e.g., diuretics) or regulate heartbeat (e.g., amiodarone) or blood thinners (e.g., warfarin) to minimize clots. Similarly, two-fifths were taking medicines to manage fluid and/or mineral levels (e.g., electrolytes, mineral and vitamin supplements.) A small number reported taking anti-bacterial treatments,

home therapies, including green tea extract, and other medicines to manage GI distress.

Overall, only three patients (all Americans) reported using Tafamadis in the past; however none were currently taking the medication. The low number is not surprising given that the therapy is not approved in the USA or Canada.

In terms of the two treatments specific for hATTR, three reported having received Tensed (inosteren), an antisense oligonucleotide (ASO) that leads to degradation of TTR; however, only one respondent was currently using the therapy.

Additionally, 29 of the respondents reported current or past use of Onpattro (patisiran), a small interfering RNA-based drug that suppresses ATTR production. Among these, two indicated they were no longer receiving the therapy.

Effectiveness: Respondents were asked to rate the effectiveness of each therapy in managing hATTR symptoms, on a five-point scaled anchored by "not at all" to "very well." Interestingly, the Canadian transplant recipient indicated that the procedure has been very effective, while the American patients reported that it was "not at all" effective. For the Canadian patient, the transplant had resolved the symptoms of hATTR to the point of stabilizing functioning and not requiring other therapies. The two patients who indicated the transplant was not effective cited no change in symptoms or continued disease progression: "…liver transplant appears to not be very helpful, with continued progression after transplant." It is not clear whether this reflects difference in type of hATTR (genetic variation) or other factors (e.g., state of disease, time since transplant, follow up procedures). One patient reported that research into liver transplant and stem cell replacement indicated neither were that effective but were also very invasive therapies. "However, fundamentally it's like using a hammer to solve a headache and it's very evasive [sic], and cause more harm than good."

Among those taking medication to manage their cardiac symptoms, most reported that the therapies worked well or very well for keeping their cardiac symptoms under control, that is, blood pressure and/or arrhythmia; however, 12% to 20% also reported these therapies were "not at all" or "poorly" effective in managing symptoms. Respondents were not very positive about treatments to manage fluid levels (with 40% on the positive side and 60% saying only "moderate" to "not at all"). Treatments to address inflammation (mainly Diflunisal) were regarded as mostly not effective, with twice as many respondents (24%) saying they were "not at all" or "poorly" effective than those indicating they performed "well" or "very well" (12%). About one-half said these drugs provided "moderate" symptom management.

The only therapy that directly addresses the cause of hATTR (excess transthyretin) was not approved for use in the USA (due to lack of demonstrated efficacy) and was not submitted to Canada; therefore the experience has been limited. However, it is not clear the degree to which the experience of the patients responding to the survey is typical of the hATTR community at large. Among those who reported using Tafamidis, two reported it had been "somewhat" effective in managing symptoms while one reported it was "not at all" effective.

5. Improved Outcomes

Perhaps most revealing of the unmet need in therapy for patients living with hATTR were the responses to the open-ended question: "Not including inosteren (TEGSEDI) or patisiran (ONPATTRO), how effective are the available treatments for hATTR?" Most recognized there were no specific therapies for hATTR: "Am not aware of other treatments." "I'm not on any specific medication for ATTR only my regular heart medication." As noted previously, medications to address cardiac-related symptoms were deemed mostly effective for that specific purpose. "My heart appears stable." "Treatment for blood pressure and fluid retention have been effective in my case."

Overall, the patients recognize therapies available have had little impact on disease progression. “They [other drugs] are somewhat effective, not sufficient changes to that noticeable.” “Diflunisal slows it down slightly not much of a help by itself.” “… we desperately need drugs that will flush out the added proteins in our system - that would help with all of the symptoms/”

One respondent summed up the experience with all of his treatments in one heartfelt phrase: “Pissin in the wind.”

6. Experience With Drug Under Review

The survey was directed to all Canadian hATTR patients and through the Amyloidosis Support Group to American hATTR patients, specifically calling upon those who have had experience with Onpattro.

Overall, the majority (75%) of respondents reported knowing about Onpattro and how it was used; indeed more than half said they knew a lot about the medication. Only a small percentage (13%) said they were unaware of the drug while a similar number indicated they had heard of the drug but were not fully aware of its use. Not surprisingly, awareness is skewed toward the American respondents, with 87% of American patients saying they “know a lot” about Onpattro, and another 9% indicating they “know about” the therapy, with only 4% saying they are only “somewhat aware.” In comparison, only one-fifth (21%) of the Canadian respondents reported they knew a lot about Onpattro and another one-third (36%) knew about the drug and how it was used. Conversely, more two-fifths (43%) said they had not heard about the drug and/or did not know how it was used. These findings reflect the fact there was only one clinical trial in Canada and the trial director was not open to approaching the patients to take part in the submission.

The Canadian patients had accessed Onpattro through clinical trials. The American patients had access through clinical trials, compassionate access, and funding through various private and public insurance programs.

Comparison to others: benefits and disadvantages and impact on patients and family: Respondents were asked to tell us, in their own words about the benefits of Onpattro. Clearly, there is absolutely no comparison between Onpattro and all other therapies. There were two types of benefits that were consistently raised. The first referenced the impact on symptoms, namely reduction in nerve pain, increase in strength and energy, better appetite, and improved mobility. The second related but distinct benefit was “slowing or halting” disease progression. Thus, in their day-to-day life, patients felt better and were able to do more. As importantly, they were optimistic that this insidious disease was being held in check, if not actually cured.

“I have more energy. My autonomic nerve issues are better. I have a more positive outlook on life.”

“I have had great benefits from Onpattro. I've been able to semi control my gastro, and at my last cardiologist appointment they we're able to see improvements, which my cardiologist has stated he has never seen...

“I can move better, easier, stronger. … in September I lost my job so I have been looking for new work since. Since I'm stronger I know I can now work in other places other than home.”

“My mood is better (not so hopeless) and my energy level better. My caregiver is also hopeful since my walking and energy symptoms are better.”

“The most important benefits is that it has stop the progression and it doesn’t have any side effect, I don’t have to suffer pain like I used to and less frequent diarrhea and constipation.”

“Prior to receiving ONPATTRO during a clinical trial, the effects of hATTR on my leg nerves and on my heart were

Fully 50% of participants receiving Onpattro reported they had experienced no side effects with the therapy.

Others said they had experienced some nausea, edema, hot flashes, chills, short headaches, and diarrhea. These are all consistent with reactions experienced to other infused biologic medicines and most were dissipate shortly after the infusion. A couple of people reported diarrhea, even “occasionally severe diarrhea that is an “exacerbation of that caused by the disease itself.” Several indicated that their side effects were caused by the medicines taken prior to the infusions, such as steroids, to minimize possible side effects to the therapy itself. In all cases, the side effects were considered to be manageanle and no one reported discontinuing Onpattro because the side effects were not tolerable.

7. Anything Else?

Individuals with hereditary amyloidosis transthyretin constitute a very small subset of amyloidosis patients. It has a profile that is not dissimilar to amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disease that affects nerve cells. As a disease, hATTR differs from ALS in many ways, such as origin and scope of impact, but it is similar in some ways. Both diseases affect the nervous system and impair mobility. Both generally affect older adults (but not exclusively). Life expectancy following diagnosis has averaged about five years. Both diseases are considered as rare (within the definition of most jurisdictions) and, therefore, have not attracted the same level of research interest and investment as more populous diseases. Until recently, there have been no effective treatments for either condition; now there are several potentially life-altering therapies. The US regulators have been among the first jurisdictions to propose new approaches to criminal criminal charges and heart.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No, the survey and analysis were conducted by the Canadian Organization for Rare Disorders

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No, we have no recollection of anyone entering the role.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Alnylam		X		

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Durhane Wong-Rieger Position: President & CEO

Patient Group: Canadian Organization for Rare Disorders

Date: 18 February 2019