CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

exagamglogene autotemcel (TBC)

(Vertex Pharmaceuticals (Canada) Incorporated)

Indication: Exagamglogene autotemcel (exa-cel) is an autologous genome edited hematopoietic stem cell-based therapy indicated for the treatment of patients aged 12 years and older with: transfusion-dependent beta-thalassemia (TDT)

May 13, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CADTH and do not necessarily represent or reflect the views of CADTH. No endorsement by CADTH is intended or should be inferred.

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CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

Patient Group Input

Name of Drug: Exagamglogene Autotemcel

Indication: Sickle Cell Disease, Thalassemia Disorder.

Name of Patient Group: Global Action Network for Sickle Cell & Other Inherited Blood Disorders (GANSID) on behalf of its Canadian member organizations listed below:

1. Thalassemia Foundation of Canada

2. Sickle Cell Awareness Group of Ontario (SCAGO)

3. Sickle Cell Awareness Network of Saskatchewan

4. Sickle Cell Disease Association of Atlantic Provinces

Author of Submission: Lanre Tunji-Ajayi, M.S.M

1. About Your Patient Group

The GANSID is a global organization registered in the USA as a charitable organization and in Canada as a not-for-profit entity. It is governed by a board of directors and led by a CEO who runs the day-to-day operations of the organization. GANSID comprises of 60 member organizations across 20 countries

In Canada, the GANSID has 4 member organizations (listed above) which are autonomous in their operations.

Website: https://inheritedblooddisorders.world/

2. Information Gathering

Data was gathered through:

a). The survey of people affected by Sickle Cell and Thalassemia Disorders in Canada

b). One-on-One conversation with people affected by Sickle Cell and Thalassemia Disorders in and outside of Canada.

Sickle Cell Disease: The Sickle Cell Awareness Group of Ontario (SCAGO) conducted a survey of 45 individuals living with sickle cell disease and their caregivers. It also held a one-on-one interview/conversation with 10 peers living with sickle cell disease. Of the people surveyed, 57% have sickle cell disease and 43% are caregivers of people living with the disease.

Thalassemia Disease: The Thalassemia Foundation of Canada (TFC) conducted a survey of 80 people across Canada including the province of Quebec. 61 of which are individuals living with thalassemia disorder and 19 are caregivers of people living with thalassemia.

The GANSID also received comments from peers living with Sickle Cell and Thalassemia Disorders outside of Canada.

3. Disease Experience

Impact of Disease on Day-to-Day Life and Quality of Life of People Living with Sickle Cell and Thalassemia Disorders:

Sickle Cell Disease: The impact of sickle cell disease on patients' quality of life are varied and differ from individual to individual. In general, sickle cell disease will affect every aspect of the affected person's life. A few examples of how it may affect someone living with the disease are provided below:

a). It may cause damage to vital organs of the body such as the kidney, liver, heart. It may also cause blindness, deafness and premature death.

b). It may cause disruption in family life balance whereby the affected spent too much time on admissions in hospitals and may not be able to manage the disease along with work and family life expectations. This may cause conflicts at home leading to higher rates of separation and divorce in marriage.

c). Frequent hospitalizations leading to absenteeism in school and work, and resulting in lost education and job opportunities. It also reduces the opportunity for the affected to contribute meaningfully to their community and society.

d). Recurrent ischemic priapism is a common morbidity among men with sickle cell disease and based on research studies, men with sickle cell disease experiences higher sexual dysfunction compared to men without sickle cell disease. Priapism affects self-esteem and self-image of the affected, leading to additional psychosocial issues. You may learn more at the link here: https://ashpublications.org/bloodadvances/article/4/14/3277/461435/Men-with-sickle-cell-disease-experience-greater

e). Sickle Cell Disease affects fertility in males and females living with the disease.

f). Many of the respondents in the survey also advised that the disease is very tiring and this is especially true when pain medication doesn't work to effectively control their pain or when healthcare providers are second-guessing the severity of the pain they are experiencing.

g). People living with sickle cell disease are often stigmatized and labelled as drug-seeking in Canadian hospitals. Without the disease, many felt that they might not have witnessed the same level of discrimination from the Canadian health care system.

Thalassemia Disease: The impact of thalassemia disorder is most felt by people living with transfusion dependent beta thalassemia major. Based on the survey conducted by the Thalassemia Foundation of Canada, this subset of Thalassemia patients has to go through recurring transfusion treatment which could be exhaustive in its own. Furthermore, the survey respondents advised that:

h). They need to orientate all facets of their life towards their transfusion cycle. A respondent stated that they need to budget 7-10 days of good health post-transfusion towards the maintenance and upkeep of family, and yet they still need to find pockets of time where one can do things that also bring joy.

i). The disorder has made them unable to participate in family activities. This could bring feelings of guilt and disrupt family dynamics.

j). Thalassemia and the continuous blood transfusion program contribute to lower self-esteem and psychological well-being of peers with Thalassemia.

k). They experience less energy to carry out day-to-day activities, exercise and attend social functions, especially as it gets closer to the time for transfusion

l). Excess iron from the frequent transfusion treatment could lodge in vital organs of the body causing damage to these vital organs and as such, patients with Thalassemia do not only go through continuous blood transfusion regimen, they also must go through iron chelation therapies.

While some patients do well on oral chelation therapies, there are those that require desferal as their chelation treatment option. Desferal must be administered subcutaneously over a period of 10-12 hours each evening. Even for

those that can take the oral chelation therapies, other side effects such as nausea, gastrointestinal issues, rash, kidney issues and lowering of white blood cells can be problematic and even dangerous.

In addition to iron chelation, a multitude of other routine diagnostic tests are required and thalassemia patients must receive multi-disciplinary care, preferably at a specialized treatment centre.

m). Having a low hemoglobin prior to transfusion also affects all aspects of life due to chronic fatigue

Impact of Disease on Day-to-Day Life and Quality of Life of Caregivers of People living with Sickle Cell and Thalassemia Disorders:

Sickle Cell Disease:

Sickle Cell Disease does not only affect the individual living with the disease but also their families and friends. Caregivers and other family members advise that due to their loved ones living with this disease, they themselves suffer from:

a). Emotional and psychological deficits. Many blame themselves for passing the gene to their child, and they experience guilt feelings, especially when their child is going through the episodic pain crisis associated with the disorder.

b). Disruption in family balance life. Given the unpredictability of the complications association with the disease, planned family activities including vacations are sometimes cancelled at the last minute.

c). Inability to work at all or full time due to their child's frequent hospitalizations as a result of the disease.

d). Depression and anxiety due to their child's illness resulting in low quality of life.

Thalassemia Disorder:

The caregivers of people with thalassemia are very much affected by the disorder and they provided that:

e). When parents of children with thalassemia receive the gut-wrenching news that their child has thalassemia disorder (usually when the child is at a very young age), they are overwhelmed with feelings of guilt that they have passed this on to their child genetically and then spend the next 18+ years caring for their child that has intense medical needs, which requires time off work and causes extensive worrying and stress. Some find it daunting, especially those new to the country who don't speak French/English and those who don't know how to navigate the healthcare system.

f). They suffer emotional pain when watching their child endure being poked multiple times to get an IV in. A respondent advised that he could see his son tensed up when he has to get his IV in.

g). They go through exhaustion due to multiple appointments including routine blood transfusions for their child. For many, the blood transfusion schedule is monthly while for others it could be less or more frequent than every 4 weeks.

h). They may incur financial stress due to time off work and out of pocket expenses for medications, travel to the hospital, etc.

i). The disorder could put stress on the whole family and also hinder family activities including vacations.

j). It is stressful to have to take time off from work multiple times a month for transfusions, and other appointments such as: MRIs, hearing and eye tests required for their child's treatment

4. Experiences with Currently Available Treatments

Thalassemia Disorder:

a). Impact on personal and social life- Patients and family members spent long days at the hospital during transfusions and other appointments, impacting time and energy left for other family and life activities.

b). Time- Iron chelation is an essential treatment for patients with thalassemia who are on continuous blood transfusion. While many do well on oral chelators, there is the subset of patients that do well on desferal which also require additional appointment and travel time to the hospital.

c). Treatment procedure- Caregivers advised that their children are not very fond of the essential but painful needle poking before an IV could be put in for treatment.

Sickle Cell Disease:

Most people with sickle cell disease in Canada are on modifying therapies such as hydroxyurea (HU) and blood transfusion treatments.

d). Hydroxyurea- This is a standard therapy for sickle cell disease. It is supplied in capsule form in Canada and would require compounding into suspension for younger patients. Unfortunately, not every pharmacy is able to support families in compounding the drug into liquid suspension. As such, family members may have to do the compounding themselves- which might not be as accurate as it should be done. Furthermore, they may also be exposed to inhaling the drug, resulting in potential health hazard for them.

e). Blood Transfusion- Peers with sickle cell disease on continuous blood transfusion face challenges around taking time off work to attend their routine transfusion appointments.

f). Limited Treatment Option- There is a subset of patients with sickle cell disease that the current treatment options do not work for and unfortunately, these patients will continue to experience preventable morbidities and premature death except there are new treatments that they could be try.

5. Improved Outcomes

Thalassemia Disorders:

Based on the survey conducted by the TFC, respondents' expectations for the new treatment include:

a). Improved Quality of Life- Families would like to no longer be transfusion dependent. A respondent also provided that they would want their daughter to spend life as normal as their peers.

b). Low Risk & Post-Treatment Support- Respondents expect this treatment to be accessible, efficacious, well researched, with a reasonable balance of risk to reward, and good support infrastructure post treatment.

c). Access- Families expect that it will be covered by the Provincial Drug Programs, and be an available option to anyone who is a good candidate for it regardless of economic means.

d). Cure- The new treatment to cure Thalassemia with no need for further transfusions.

e). Safety and Efficacy- The new treatment will be safe and effective.

Sickle Cell Disease:

Based on the survey and interview conducted by the SCAGO, respondents' expectations for the new treatment include:

f). Risks and Side Effects- Families are happy for a cure, however, they expect the benefits of the cure to outweigh the risks and side effects. According to some respondents, the long-term safety of these therapies should be explored and the proponents of these treatments must provide empirical evidences of outcomes and long-term effect on participants.

Many of the respondents would also like to see that the new treatment has reduced risks especially around immune systems and fertility.

g). Ease of Access- Families expected the new treatment to be accessible to individuals who desire to explore it as a treatment option regardless of financial means.

h). Improved Health Outcomes- Families expect the new therapy to eliminate the pain crisis and end-organ damage experienced by people living with the disease.

i). Lasting solution for all: Families expect the new treatment to cure sickle cell disease and free all from any complications relating to the debilitating disease.

6. Experience with Drug Under Review

Sickle Cell Disease: None of the patients surveyed or interviewed by the SCAGO had experience with the drug under review.

Thalassemia Disorder: None of the patients surveyed by the TFC had experience with the drug under review

7. Companion Diagnostic Test

None of the patients surveyed and interviewed had experience with the drug nor biomarker testing regarding the drug under review

8. Anything Else?

As a global organization supporting people affected by hereditary blood disorders, the GANSID believes that the world is in exciting times where sickle cell and thalassemia disorders are concerned.

This is especially true with many pharma having increasing interest in hemoglobinopathies and developing innovative cure therapies in this space. However, access to these therapies may be hindered due to funding for the therapies from country level health systems.

The GANSID is of the opinion that the lifetime costs of sickle cell and thalassemia disorders to the persons living with these life-altering diseases and their family members (not limited to the cost of treatment, admissions in hospitals, loss of school and work times, loss of productivity in society, disrupted family life balance, and mental health deficits) is far more expensive than the cost of the new treatment.

As such, the GANSID is submitting to CADTH that it is in the best interest of the people with sickle cell and thalassemia disorders as well as the Canadian Health System to ensure:

- the safety of the new treatment;

-access to the new therapy by patients who are good candidate for it.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, 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.

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

No

1. 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

2. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range with an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Vertex Inc			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: Lanre Tunji-Ajayi, M.S.M
Position: President/CEO
Patient Group: Global Action Network for Sickle Cell & Other Inherited Blood Disorders (GANSID)
Date: May 11th, 2024

Patient Group Input

Name of drug	**exagamglogene autotemcel**
Indication	**Transfusion-dependent β-thalassemia**
Name of the patient group	**Thalassemia Foundation of Canada (TFC)**
Author of the submission	**Josephine Sirna with input and review from board members of the TFC, Vancouver Thalassemia Society of B.C. and community volunteers**
Name of the primary contact for this submission	**Josephine Sirna, Vice President, TFC**
E-mail	[redacted]
Telephone	[redacted]

1. About Your Patient Group

Thalassemia Foundation of Canada is a volunteer-run charitable organization established in 1982 as a support group and eventually incorporated as a Canadian charity in 1988. The mission of the Thalassemia Foundation of Canada (TFC) is to support and fund thalassemia scientific research, treatment, patient services, public awareness and education.

The goals of TFC are:

- To provide patients and caregivers with accurate and up-to-date information on thalassemia research and treatment.
- To help patients and their families navigate through the healthcare system, acting as advocates for themselves and others.
- To provide practical and beneficial resources and support services to the thalassemia community.
- To further research and innovation in thalassemia treatment and care.

Its Board of Directors is made up of individuals with valuable skills and lived experiences (primarily made up of patients and caregivers) who represent the thalassemia community across Canada - with board members from major thalassemia centres like Toronto, Vancouver, Montreal and Ottawa. We collaborate with the Vancouver Thalassemia Society of BC and are supported by the Guelph Chapter.

TFC is an active member of the Thalassemia International Federation (TIF) which is officially recognized by the World Health Organization, and our President sits on the Board of Directors for TIF. TFC is also a member of the recently formed Global Action Network for Sickle Cell and Inherited Blood Disorders (GANSID). We work in collaboration with health care providers in Canada's thalassemia comprehensive care treatment centres, the blood system operators (Canadian Blood Services and Héma-Québec), the Network of Rare Blood Disorder Organizations, the rare disease community, and others who share our common interests.

Charitable Registration #: 119068492 RR 0001

Website: Thalassemia Foundation of Canada - Home Page

CRA Quick view for Thalassemia Foundation of Canada

2. Information Gathering

As part of our information gathering for this submission, we used a combination of methods: we surveyed our patient and caregiver population across Canada in April 2024 and also looked back at prior surveys conducted in 2022. Two patients and three caregivers were part of the sub-committee that prepared the survey and this submission and were able to add their personal experiences as

needed. The 2024 survey was distributed through sharing on Thalassemia Foundation of Canada social media platforms, email e-blasts to established distribution lists and personal communication from the sub-committee to known thalassemia community members.

The most recent survey results came from 80 respondents across 5 provinces (British Columbia, Alberta, Manitoba, Ontario and Quebec) and were largely representative of both the Canadian population distribution and the thalassemia community distribution (see table 1). About ¾ of the respondents were thalassemia patients and the remaining quarter were caregivers of a patient who were instructed to answer as from the perspective of the patient (see figure 1).

Table 1: Distribution of patients/caregiver survey respondents across Canada

Province	Percentage	Number of Respondents
British Columbia	33.75%	27
Alberta	6.25%	5
Manitoba	1.25%	1
Ontario	45.00%	36
Quebec	13.75%	11

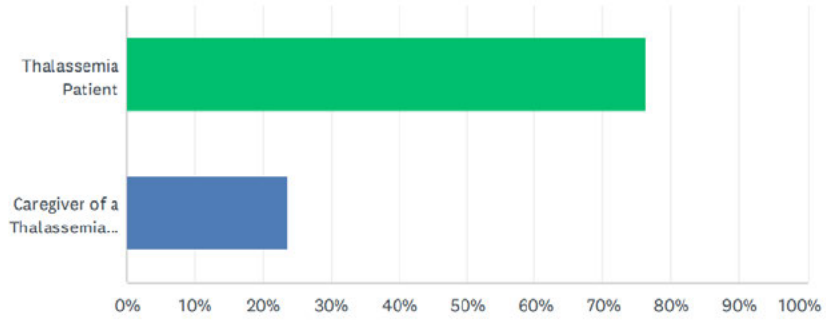

Figure 1: bar graph depicting distribution of patients or caregiver respondents

There was a wide distribution of respondents across all age groups (see Figure 2). The vast majority of respondents were 25+ years old, in addition to 10 respondents stating to be in the 0-11 years old category.

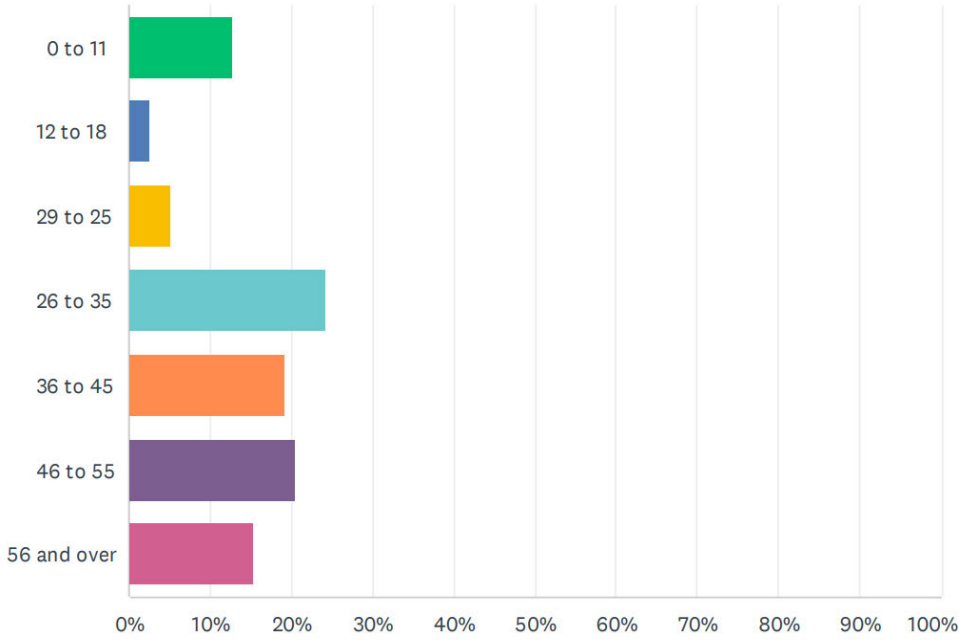

Figure 2: Age distribution of thalassemia patients who (or whose caregiver) completed the survey

Although the survey was intended to focus on the responses of transfusion-dependent beta thalassemia (TDT) patients, patients of different genotypes were also welcome to respond. Figure 3 depicts the distribution of responses based on the patient's diagnosis/genotype, with transfusion-dependent beta thalassemia being the highest response (>90%).

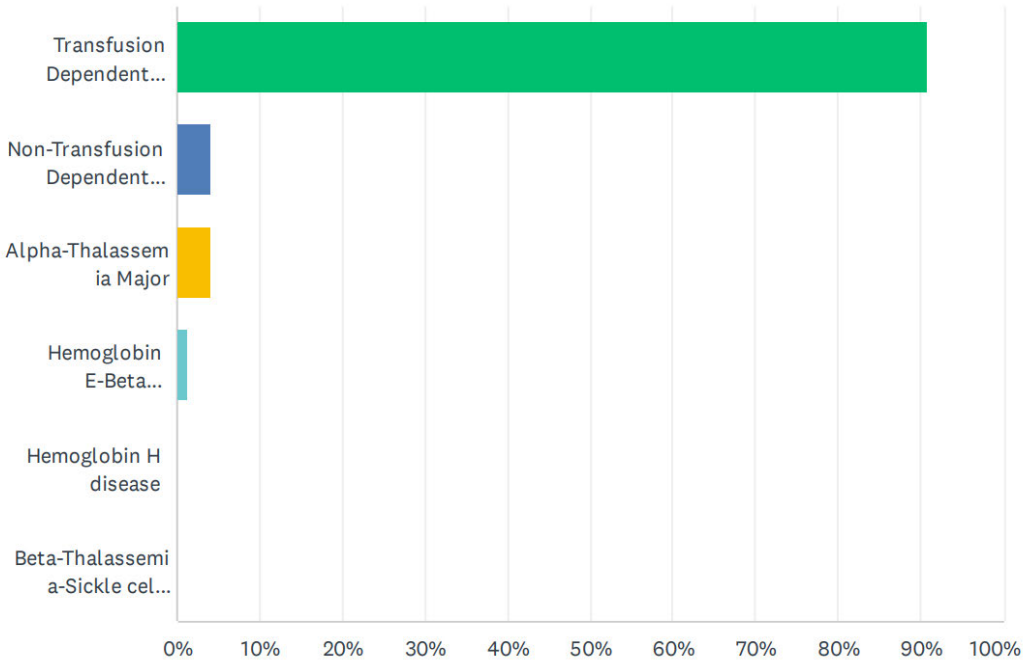

Figure 3. Thalassemia diagnosis of respondents

In addition, we reached out to patients/caregivers that have experience with the treatment under review (exagamglogene autotemcel) through personal connections, private Facebook groups and gathered other information from the Children's Hospital of Philadelphia (CHOP) Thalassemia Patient Stories website CHOP Thalassemia Center Patient Stories.

3. Disease Experience

Thalassemia is an inherited blood disorder that has both physical and psychological consequences. The patient experience is all encompassing. It is not an exaggeration to say that the disease touches every aspect of their lives, all the time.

In order for a child to be born with β-Thalassemia, both parents must be carriers of the β-globin mutation. f If both parents are carriers, there is a 25% chance with each pregnancy of having a child with Transfusion Dependent Thalassemia (TDT). In Canada, TDT is considered a rare disease, however the impact on the patients, their families and our society is significant. We will describe below both the physical and psychosocial manifestations along with the significant consequences on society.

The genetic aspect is important because from the moment of diagnosis, parents are faced with the guilt of passing along a potentially deadly disease to their baby. There is shame in having passed

along a burden to their child and there is also disappointment and fear of the unknown health issues ahead, especially since they are told there is good treatment in Canada but it is life-long. Parents have passed along a ball and chain to their TDT child, who is now tied for life to a hospital for transfusions. On the other hand there have been TDT families who have placed the psychological burden on their children advising them to hide their illness or not divulge it to friends or extended family. TDT patients also experience times of frustration and anger that sometimes is aimed at their parents due to TDT being an inherited ailment.

Physical Impact:

A child born with TDT produces either a very small amount of hemoglobin (β^{+}mutation) or none at all (β^{0}mutation); hemoglobin is used by red blood cells to transport oxygen throughout the body. Without proper treatment in the first years of life, TDT patients are severely anemic, lethargic, tired, feel short of breath and feel weak. Symptoms, if they are not treated, cause a patient to deteriorate and it affects their whole body; ultimately an untreated TDT patient would die before the age of 5 due to severe anemia causing heart failure.

There are various forms and genotypes of thalassemia, the more severe ones requiring the most demands for treatment and monitoring (regular blood transfusions every 1-5 weeks (see Figure 4).

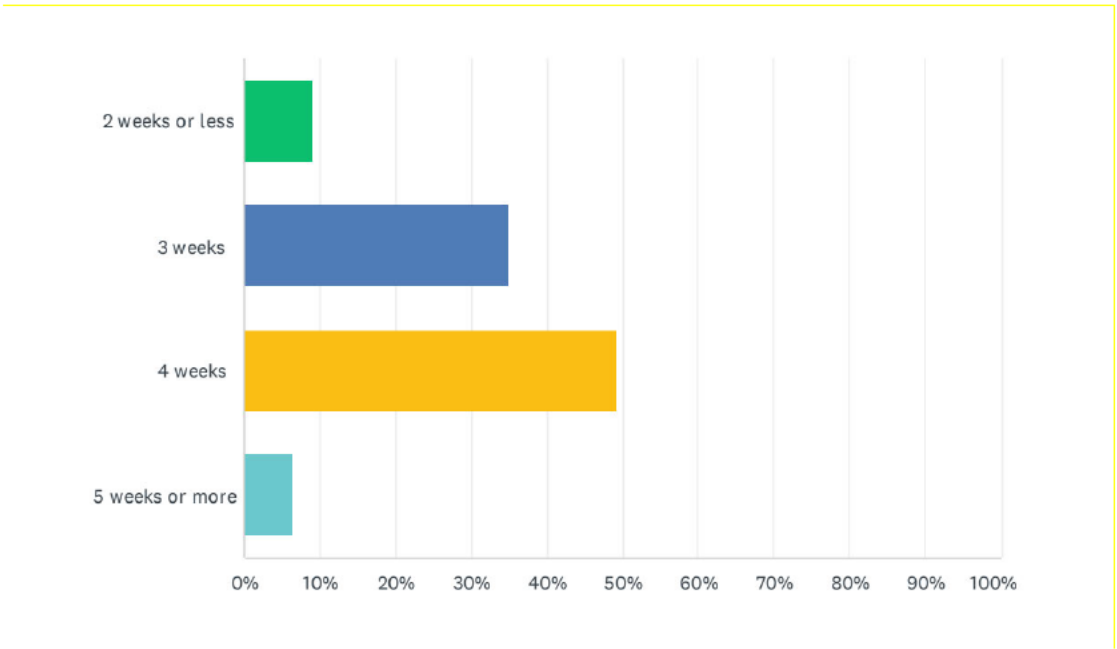

Figure 4: Average blood transfusion schedule routine

They also required daily iron chelation, regular blood testing, regular diagnostic testing, regular monitoring by a large number of doctors of many specialties annually, etc. (see Figures 5 to 7 & 10)

This involves multidisciplinary (Figures 5 & 6) care normally arranged at a comprehensive care centre, which are typically only located in Canada's major city centres (e.g. Toronto, Vancouver, Montreal, Calgary, Edmonton, Ottawa, Winnipeg, Hamilton, etc) where medical schools are located. For patients who live remotely, access to comprehensive care is an ongoing concern. Apart from the hematologist or pediatrician, patients also see a number of specialists and each specialist represents a separate clinic visit and monitoring tests for the TDT patient (Figure 5). For those that responded "other", the following categories were identified: Nephrologists/urologists, physiotherapists and hepatologists (liver specialists).

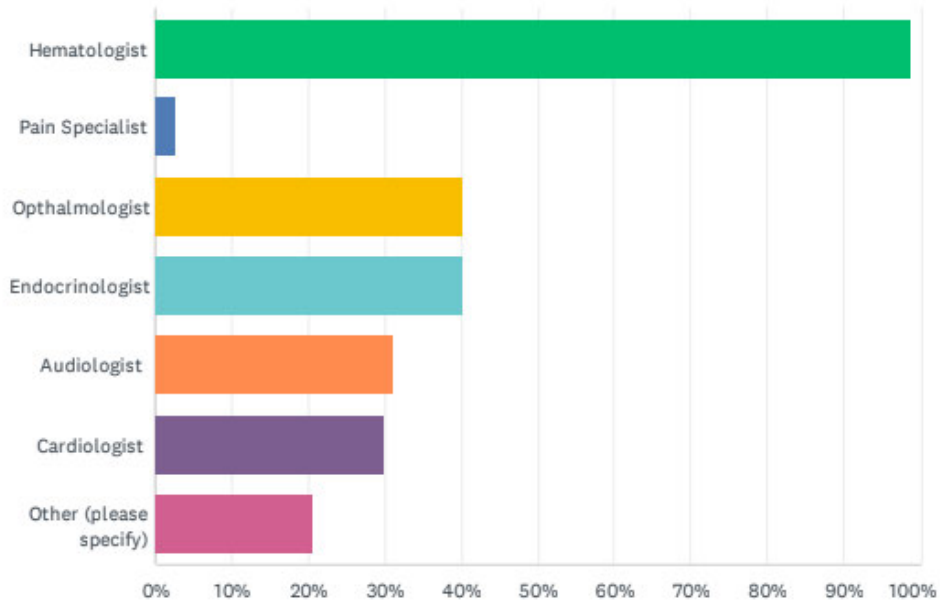

Figure 5: What medical specialists that patients regularly visit

Figure 6 below shows the other healthcare professionals that patients need as part of their care team making it even more complex to navigate the healthcare system.

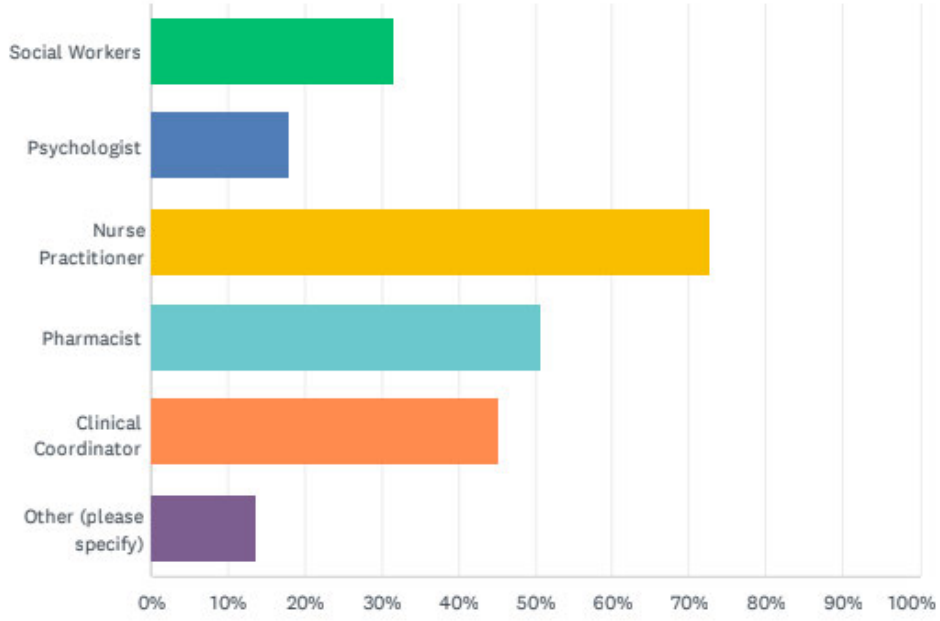

Figure 6: Other members of the Thalassemia healthcare team

The challenges and limitations a person with TDT has are many and has evolved over the years. For starters, to keep hemoglobin levels at an adequate level, the basic treatment is regular blood transfusion. Patients receive the necessary quantities of red blood cells (~15 ml/kg) which are collected from whole blood donors, filtered, separated into components, tested and screened for infectious diseases by the blood operators in Canada (Canadian Blood Services and HemaQuebec) and delivered to hospital blood banks. In hospitals, the donated RBC units are controlled and cross-matched with the patient's own blood to avoid allergic or severe rejection reactions. Adults receive an average of 13 transfusions and 39 units of blood per year. The amount of blood may vary for some patients. Generally the amount of blood transfused is based on weight, age, cardiac health and other factors. For example, a patient at 50 years old may have received approximately over 500 transfusions and over 2000 units of blood. To date, there is no cure so this regimen and number of transfusions and units of blood will continue to increase.

Receiving that many transfusions is very onerous:

Besides the discomfort and pain from intravenouses (IVs) for blood transfusions, patients can experience water retention causing bloating, back pain, etc. Transfusions also take time (e.g. 6 to 9 hours (or one full work/school day) every four weeks) and require time off work and school for caregivers and patients. Receiving blood transfusions also introduces risks of known and unknown pathogens and unfortunately thalassemia patients have been historically impacted by tainted blood

products (e.g. contracting hepatitis C virus through tainted blood transfusions in the 1980's and 1990's). Some patients also deal with blood reactions, allergies to blood and hemolysis making blood transfusion complicated and potentially very dangerous. Many patients have had their spleens removed (splenectomy) to effectively manage ongoing blood requirements. Although splenectomy is required to stop the overactive spleen from destroying transfused red blood cells, spleen removal introduces a life-long inability of the body's immune system to properly fight infection.

The most serious and common side effect is the body's eventual overload of iron (secondary hemochromatosis). Iron overload is responsible for most of the complications patients face in TDT, including causing damage to vital organs and leading to comorbidities such as infertility, heart disease, diabetes, cirrhosis of the liver, thyroid and parathyroid dysfunction, etc. To deal with it, TDT patients require life-long treatment with iron chelation drugs.

Some patients take deferoxamine - a drug infused subcutaneously 10-12 hours a day, 7 days a week (Figures 11 to 13). This can cause swelling and heated inflammation at the site of infusion (arms, legs and stomach). As a result, some patients choose to have a portacath or Picc line implanted to infuse the drug 24/7 intravenously (Figure 14).

Others are able to take oral medications and while that might alleviate the daily needles and infusions, there are other side effects and issues that have transpired for patients with these drugs.

Desferosirox can cause severe gastrointestinal issues including, bloating, cramps and diarrhea. Leading to both physical and emotional trauma as dealing with these symptoms can be extremely difficult and embarrassing at work and school and may interrupt sleep. Another common reaction patients may experience is rashes..

Deferiprone is another drug but it too can have side effects such as nausea or in some cases cause arthropathy and neutropenia which can lead to serious medical issues, therefore patients need strict monitoring during therapy.

All three iron chelator medications are intense and need regular monitoring for side effects, which is done systematically by a comprehensive care unit and team of health practitioners.

Another consideration is availability, accessibility and affordability of the drugs and treatments. Shortages of deferoxamine are a current issue, drugs are extremely expensive (e.g $100k a year) and for patients with private coverage lifetime maximum of $1M create grave concern of how these drugs will be covered long term.

Thalassemia can also cause other health issues including loss of bone density (e.g osteopenia or osteoporosis) and higher risk of liver cancers, etc. As a result, it is extremely important that patients

strictly adhere to the transfusion, iron monitoring and control programs which is difficult to do decade after decade. With all of these factors at play, many things can go sideways and cause life altering issues. For example, a patient who missed their weekly monitoring blood work for reduced white blood cell (WBC) count (an adverse effect of Deferiprone) experienced a drop in WBCs and became severely ill with a rare fungal infection that infiltrated their heart, brain and lung. This patient who worked full time and travelled extensively nearly lost their life, was in and out of hospital for two years, including spending six months in an ICU. They suffered a series of seizures and strokes, and required heart, brain and lung surgery. This illustrates how one little slip in the TDT monitoring regimen can have deadly .This person's life nearly was cut down while in their prime. Similarly, iron overload is stealth. Patients who skip their iron chelation medicine, common in deferoxamine, over a long period of time will not feel unwell but heart failure can come on suddenly. Despite best efforts to correct heart failure the reality is that iron damage of the heart is very difficult to reverse. It has been likened to falling down a cliff, it is very hard to climb back up. Unfortunately many patients in Canada succumbed to this fate, many in their 20s and 30s.

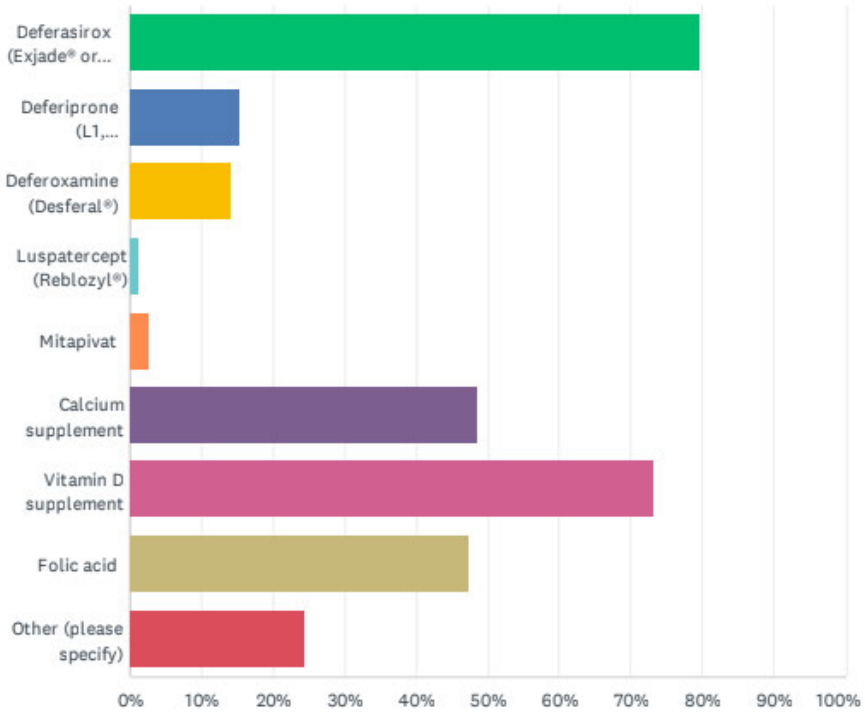

Figure 7. Medication(s) taken by TDT patients

For those that responded "other", the following categories were identified:

- Hormone therapy (e.g., birth control, testosterone, levothyroxine, estrogen/progesterone);

- Pain medications (e.g.,duloxetine, NAIDs, opioids);
- Immune therapies (e.g., hydrochlorothiazide, asthma inhalers, antihistamines); and
- Bone density (e.g., prolia, bisphosphonates).

Psychological Impact:

Thalassemia and its treatment often have numerous psychological effects on patients. Due to the social stigma of having/being a child/person with a hereditary disorder, many patients and caregivers choose to only inform a limited group of family and friends about their illness, creating feelings of isolation and despair.

Many patients experience growth delays, bone deformities and other physical changes due to anemia, iron chelation side effects and hormone insufficiency. The physical manifestations of anemia and iron overload are psychologically significant as they may affect self-esteem, distort body image, and create feelings of inadequacy. Low self-esteem and negative body image impact both mental and physical health, making individuals less likely to accept positive feedback and comply with life-saving but difficult treatment.

TDT patients may be susceptible to depression, anxiety and other mental illnesses. The lack of self-confidence may hinder social and supportive relationships and coping strategies that are needed to manage the disease effectively. Mental and emotional illness secondary to thalassemia require support from mental health professionals such psychologists, counsellors and psychiatrists.

Some of the psychosocial effects thalassemia patients experience include:

Mental and Physical Exhaustion: transfusion-dependent thalassemia patients receive blood transfusions every 1 to 4 weeks. They are constantly learning to function at different hemoglobin levels and during the days before a transfusion they may experience fatigue, pain, cognitive impairment and irritability. This impacts their performance in physical endeavours, in their education and career as well as their participation in social activities. The pain, exhaustion and disappointment of not being able to function optimally may create frustration.

TDT patients may experience growth delays, often falling several years behind their peers in height, strength and development. Patients often describe feeling embarrassed being smaller and at a disadvantage physically when participating in athletic activities with others their age.

Repeated IV pokes, subcutaneous needles that remain under the skin for 10 to 12 hours each night, pills that may cause nausea, vomiting and curb appetite, bone pain and exhaustion from

anemia can result in trauma for patients. The below quotes came directly from TDT patients and help describe these challenges:

> "Fatigue is a constant, extreme back pain the week before my treatment, sometimes stomach pain from my meds, and I need two days to recoup after my treatment."

> "Thalassemia makes me have lower energy levels generally but most pronounced in the week before my blood transfusion. I just cannot accomplish as much as others due to my lack of energy which causes me to feel upset. It creates a lot of stress in my education and work life because it is difficult to have to take a weekday off every month on top of regular sick days. I have a lot of scarring on all areas of my arms from constant needles and poking. I have to travel very far to get to a hospital that can provide transfusions which is a stressor every month."

> "The pain of watching your child endure being poked multiple times to get his IV in. I can see my son tense up when he has to get his IV in."

> "I feel very weak a day or two before my transfusion. The treatment itself is cumbersome and saps all of my energy. It feels like a shock to my system. I feel very out of sorts after my blood transfusions and it takes at least a full day for me to recover. I sometimes don't have the energy to go to the office on transfusion weeks."

> "Feeling fatigue closer to transfusion day can limit one's ability to participate in physical activity or work. Travel needs to be arranged around transfusion days and because of the numerous medical appointments involved, time off work if needed to accommodate that. One does adapt but the biggest effect is being able to fully participate in exercise of sports especially as one ages and feels the effects of the condition more and more."

Emotional Distress: The chronic nature of thalassemia, with its lifelong treatment requirements and potential complications, can lead to emotional distress in patients. Constant testing, which includes labs, MRI scans, echocardiograms and various other tests create constant anxiety as patients must strive to maintain certain levels of various parameters to protect their organs. They may experience feelings of anxiety, depression, or fear about their health and future.

> "Constant worry of being near or close by in case in need further follow up. Always need to aware of where and how many pills I have for my treatment. My health plan only supplies me with 30 day supplies which limits my ability to travel to Europe to visit family."

> “My son had needle phobia, so at one point, it was challenging to get him to take desferal every night. It was mentally draining to enforce the desferal when he was upset.”

> ”Having Thalassemia and depression and anxiety is difficult because it’s hard to discern what fatigue I am struggling with”

> “I have to use my sick days for work when I have transfusions. It doesn’t leave many days in the bank in case I do get sick. Being born with Thalassemia has perpetuated childhood trauma which means lifelong therapy to treat depression and anxiety. I was unfortunate to contract Hepatitis C in the 1980’s which involved extensive, painful, and life-halting treatment. This furthered my anxieties and it has affected my work, social life, and enjoyment of life.”

> “I feel like has affected my sons growth even thought no correlation He feels like he is smaller then other children and asks if it’s cause of the thalassemia Hate to see him have to struggle with that He does get tired near end of transfusion timelines”

Stigma and Discrimination: Due to misconceptions about the condition, thalassemia patients may face stigma and discrimination in various aspects of their lives, such as education, employment, and social interactions. This can contribute to feelings of isolation and low self-esteem. Patients may struggle with whether and how much of their illness to share with peers. As thalassemia is a rare illness, many people will not understand the nature of the illness.

> “As long as I receive blood transfusions on time, I'm good. As long as I receive chelation drugs on time, I'm good. It definitely gives me anxiety and I can't be open about it with my friends, for the fear of being treated like an outcast.”

> “missing working for treatment. people always asking questions why you look so tired. always worrying about your test results.”

> ”Limited on things to do with my child. Self confidence Limited self care due to 24 hour treatment.”

Impact on Relationships: Thalassemia can affect relationships within families and social circles. Family members may experience stress and guilt related to genetic inheritance, financial burdens, and caregiving responsibilities. Additionally, patients may struggle with forming and maintaining

relationships due to concerns about their health or fear of rejection. Irritability during times of fatigue and pain can also harm relationships and distance patients from friends and family members. Young adults may become rebellious, and refuse to comply with treatment. This can create stress and anxiety for the entire family. Relationships between patients and family members can become strained and stressed as young adults learn the responsibilities of caring for themselves. The impact of mismanagement of thalassemia may not be evident until considerable harm has occurred, therefore some young adults may endure serious complications while rebelling against their parents. As mentioned previously, once a health decline has occurred, it is very hard to climb back up that cliff. The parents who have managed the condition for many years often understand the risks, which causes them great stress and anxiety. The patients may resent their parents for worrying or interfering which can damage their relationships. The harm often extends beyond patients and often impacts the physical and mental health of immediate family members.

> “Exhaustion, managing work and numerous full-day transfusion appointments, overnight chelation makes social events difficult, low hemoglobin before transfusions can create irritability, family relations suffer because thalassemia is a topic of discussion.”
>
> “I am constantly fatigued. Often in pain. Often anxious and stressed. Sometimes depressed. But I manage to function quite well and my personal struggles are not regular noticed by others I'm close to.”
>
> ”Treatment affects the entire family, parents worry, grandparents worry, sibling grew up spending long days at the hospital during transfusions. Worry causes parents to also develop stress related ailments”
>
> ”I feel guilty and selfish every day, subjecting my loved ones to care for me. The medical costs are so high my younger siblings didn't get as much attention, compared to me, from our parents.”
>
> “Of course. I live with my mom who feels at age 80 that I am fragile because of my condition. My sister too was very affected emotionally. It is not easy on all people around you that care for you.”

Educational and Occupational Challenges: The demands of managing TDT, including frequent medical appointments and treatments, may interfere with educational and occupational goals. Patients may struggle to attend school regularly, participate in extracurricular activities, or pursue career opportunities, leading to feelings of frustration and inadequacy. The many absences from

school and work may create more work and responsibility on patients to catch up. Patients often miss many special events and opportunities because of these absences.

> “I have to schedule life around my thalassemia. Whether it's work, meetings, social events, travel, when I work out, it all has to work around my appointments, transfusions, and how I feel.”

> ”When my hemoglobin is low each month prior to my transfusion I don’t feel I have the energy I need to work, take care of my family, exercise, do housework, etc. I also need to take 13 days off work for transfusions alone, plus time off each month for cross-match activities plus other diagnostic tests. After each transfusion I typically feel chest fullness and bloated and need to go straight to bed when I get home. On a daily basis, I take 9 pills (3 pills, 3 times daily). This is a huge improvement from my childhood experience. From 5yo to 28yo I did nightly injections/infusions over 10 hours. Then from 28 to 37 When I was taking IV desferal via a portacath, I was walking around with a needle in my chest 24/7 and needed to shower and sleep with a medical pump attached to me which was difficult physically and mentally. I have become allergic to one of the approved treatments and I fear that could happen with my current oral medication.”

> “Although my employer accommodates my monthly transfusions and my many, many medical appointments I sometimes feel inadequate or that I could be perceived as a bad employee for having to be absent from the workplace. Employers say they understand but, really, I feel they tire of this illness that never resolves. I also feel that my career advancement has been hindered due to my needed accommodation for life-saving treatment.”

Coping Mechanisms: Despite the challenges they face, many TDT patients develop effective coping mechanisms to manage their condition and improve their quality of life. These may include seeking social support from peers and healthcare professionals, engaging in activities that promote mental well-being, and participating in patient advocacy initiatives to raise awareness and reduce the stigma surrounding thalassemia. Through our survey, we found that much more support is needed for our patients.

Resilience and Adaptation: Thalassemia patients often demonstrate remarkable resilience and adaptation in the face of adversity. They learn to navigate the complexities of their condition, advocate for their needs, and find sources of strength and hope to persevere through challenges.

The response from patients shows that the disease is affecting many aspects of their lives. Our survey of 81 patients shows top issues like Work (76%), Ability of travel (72%), Social life (59%), Family obligations (58%), Finances (46%), please see Figure 8. Other issues identified included: Self care, Education, Ability to Exercise and sexual/reproductive health.

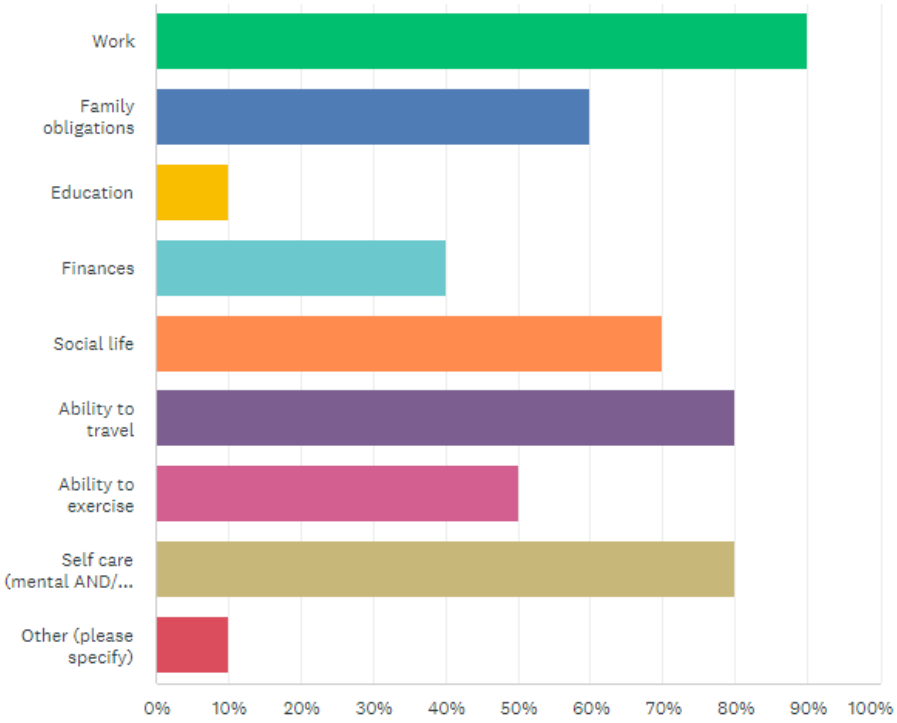

Figure 8. Areas of patient's life affected by TDT treatment

Throughout personal testimonials we heard about the burden of the current treatment, the anxiety associated with having a life-long disease and limitations in one's life due to the requirements associated with the disease, treatment, and management in a health care system that is not always accessible. Patients with TDT and their caregivers attempt to attain a "normal life" despite physical, financial and societal barriers. The burden of the disease is life-long.

Our patients and caregivers told us about their day-today life experiences:

> "My life revolves around the treatment. I love to travel but i cannot travel to a country more than 21 days. Also when i was moving abroad i had limited options. Besides travel i also feel very low in energy before my transfusion day. Some days are difficult than others. I cannot

tire myself with excessive physical exercise. However without the treatment I cannot stay alive so i am grateful to be able to access it. Its essential. I am grateful for the nurses, doctors, pharmacists and Thalasemia society."

“Being transfusion dependent beta thalassemia major, I need to orientate practically all facets of my life towards my transfusion cycle. This requires careful and considered planning around not only time but also energy. I have to somehow budget the 7 to 10 days of good health I have post-transfusion towards the maintenance and upkeep of my home, my diet, and somehow still find pockets where I can do things that actually bring me joy. And because I need to work in order to live, my budget of energy goes almost entirely towards maintaining that ability to work, and leaves me with such little leftover for the aforementioned things.”

“the medication was administered via the pump, it affected me more. I never wanted / or was allowed to go out. Having the pills now is a lot better. I often worry or wonder how things will be as I get older.”

“Being transfused is hard, takes over your life and stops me when I am on a roll. I enjoy my life and every 30 days my life comes to a halt...I am weak, tired, cranky I get transfused rest get physically and mentally sick and after about 48 hours of my transfusion I start my life all over again!”

“limitations on work, social life, pain management, we do not use pain killer but pay for chiropractor and physio for better pain management.”

“some days are normal but on other days, (especially the last few weeks before transfusions), my energy and alertness levels can wane. I do work a fairly physical job so I just have to be more aware on those days and maybe slow myself down. I also only work part time because of all the time I need for various appointments. Days before and after transfusions seem to be the worst for this and I would say its sort of like bad jetlag”

“Good days and bad. Longer to recover after being older now with so many transfusions.”

“Impacted pregnancy with regular transfusions.”

In addition we asked respondents about their quality of life. Patients and caregivers spoke of lower quality of life, complications of the illness and its treatment; they talked about experiencing fatigue, having strained relationships and dreams unfilled in part due to an arduous, unending tether to the hospital and treatments. People talk about missing work or school or using vacation days for their life saving treatment and having nothing left available for rest or pleasure. Our patients face costs and exorbitantly priced medication that they can not afford without sacrifice. There are patients who

are reliant on provincial drug plans or pharma patient support programs in order to access chelation therapy. Below are some of the personal testimonials received when patients and caregivers were asked how thalassemia treatment affected their quality of life and how it affected the life of their families or caregivers:

> “Limited on things to do with my child. Self confidence Limited self care due to 24 hour treatment.”
>
> “Not too much, but I can't travel beyond 4 weeks somewhere and I cannot live in developing countries for work, which is something I would love to do.”
>
> “The treatment has improved over years, so quality of life has also improved over years. like for example I used to get injections for iron chelation. Then I used to get those soluble tablets which felt like chalk in the mouth.but now it’s just 2 1/2 blue pills each day in the morning, so it’s pretty simple now. I feel red cross blood quality has also improved over several years. by blood quality, I mean the screening process of blood. however, due to Thalassemia, the quality of life definitely is low in comparison to any normal person because you have to go to blood transitions every 21 days. Take medicines. I feel weakness before transfusions and lethargic many times during the month. I have to take extra time for transfusions and lab Appointments and extra tests each year.”
>
> “It has obviously and negatively impacted my quality of life. Life with beta thalassemia is a life of disability. And over the years I have also acquired other comorbidities that add to the burdens that I have to shoulder in order to live something that remotely resembles a normal life. as I get older I think about what my overall expected years of quality health will be, whether I will successfully make it to retirement age, and weather I will acquire more conditions as time goes on.”
>
> “The biggest impact thalassemia has on my quality of life is by applying limitations to what can and can’t be done without appropriate planning. Example, vacations and ability to travel for extended periods of time are either worked around appointments or limited, health risks play a greater role in decision making, relationships may be strained, etc.”
>
> “My QOL has been fine. I know my limitations and live with them. Do I love it? No. Sadly, I was never able to have kids. Probably my own fault related to iron overload due to my non-compliance as a teen. I'm not as athletic as I would have liked to be. My desferal injections caused disfiguring scars to my arms and legs that I hate to this day. I lead a normal life. I have never let my thalassemia be a crutch. I have always worked full time, I am as active as

I can be, I did well in school and completed my MSN/NP. I worry a lot about retirement and being able to afford my medications. That is my biggest burden at the moment."

"Because I don't have to go for transfusions as often, and my ferritin level has improved, I am not as concerned regarding the iron overload. I am able to rest and have a weekend on my free transfusion days and I can enjoy more red meat. I no longer need to take Jadenu because of the low level of iron therefore I have not been feeling nausea, having upset stomach or sleepless nights. However, the fatigue level remains the same and it includes pain symptom management (more towards muscle and headaches)."

"It has definitely negatively affected my quality of life because it has take me away from so many family and friend commitments and makes me feel like I can't have a regular full -time job because I am worried about having to take so many days off."

"Feeling that you are tied by a chain: It is difficult to travel or be away from the hospital for more than 4 weeks. Unable to care for my ageing parents. Unable to take vacations because all are spent on Transfusions. If the clinic would open on weekends, that would help a lot."

"I am trying to figure out the best transfusion schedule. Right now, I often feel horribly before my treatment. So, my quality of life is poor before I get treatment."

"I have to weigh my decisions about how often I go out and how far I can go. When I do something impulsively or for too long, I pay for it later because I am quite tired. I can't do as much and have to plan what I do. So I miss out on things I would like to do because collectively, it's too tiring on my body. I have concerns about how long I can work and the cost of living. There are things I would like to do but it's not possible or not easy to arrange."

"Thalassemia has been a very difficult and painful life as I've had approx. 585 IV transfusions, over 10,000 needles (nightly infusions and bloodwork) and countless hospital visits and diagnostic tests. Plus bone marrow taps and liver biopsies, a splenectomy and countless hospitalizations. It's also comes with uncertainty of health, significant accommodations needed at school and work, high risk pregnancies, and overall fatigue and worry. I also had to leave my secure employer after 24 years because my insurance coverage for my expensive medication ($100k a year) was causing me to get near my lifetime maximum. I also worry I won't be able to retire early (which I feel I will need to do

because of my health concerns and reduced energy) because I won't be able to afford my expensive medications."

"do not have normal life and healthy people do not understand our challenges and expect us to do all things similar as a healthy person does"

"I grew up in a hospital so I didn't realize that it was unusual until I got older. I know there are worse diseases/disorders so I feel lucky in some ways, but it still is alot to deal with at times, especially as I get older and the all responsibilities that come with that. I do only work part time, which is a choice we made as a family, but I know it puts more pressure on my wife and kids as they are getting older."

"My son needs to skip school every 3 weeks and as a parent I need to take time off every 3 weeks as transfusion is only Mon to Fri. We live in Coquitlam and will take us an hour each way to commute back and forth."

"I don't have a particular caregiver , but my family is my caregiver. their life has also been affected by my condition because they have to be more careful by making sure that they don't exert me much. Also, also, they travel plans might get affected due to the transfusion. My boyfriend always comes with me in my transfusion, so he also take time off his week.

"Having thalassemia put a lot of pressure on my immigrant parents to quickly learn to navigate the healthcare system to help me get the care I needed. I lived outside of Toronto where the thalassemia centers were so it required them to travel a lot back-and-forth to the hospital for sick children. My parents had to learn how to do the nightly injections starting when I was five years old. When we would want to travel in the summer to Greece where my grandparents lived, they had to coordinate healthcare there including out of pocket expenses. My siblings (especially my sister who I shared a room with) had to watch me get my nightly injections and help me when I wasn't feeling well or I had regular medication lumps on my arms and legs from the infusions."

"I've been very lucky to have such caring and patient parents and siblings. (and also extended family and friends!) It has been alot of sacrifice for them, especially when I was young. I'm sure there are many sleepness nights and angst for parents with children that are sickly or need frequent medical care. I'm sure there were many cancelled trips, plans and even activities that my family could not afford or participate in because of me."

Patients and caregivers do what they have to do to stay alive and they try very hard to live normal lives but that does not mean it is easy or enjoyable. People are coping the best they can with the treatments they can access but there are expenses and side effects and personal costs that many patients are encountering.

Patients and caregivers were asked how their health today compared to two years ago. Over 50% of patients felt that their health is the same as before and 25% felt it is better but, unfortunately, there are patients who feel their health is worse than two years ago (Figure 9)

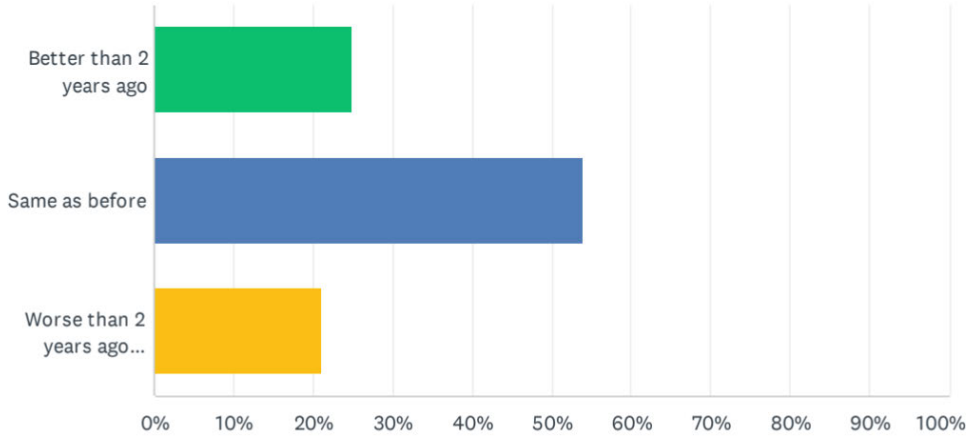

Figure 9. Considering your current treatment, how do you rate your health progress?

4. Experiences With Currently Available Treatments

Living with TDT requires lifelong management, including regular blood transfusions, chelation therapy to prevent iron overload, and comprehensive monitoring of various parameters to detect and manage complications. Adherence to treatment and regular follow-up with healthcare providers are essential for maintaining quality of life and reducing the risk of long-term complications.

Treatment Guidelines (see Consensus Statement of Clinical Care of Patients with Thalassemia in Canada) were published through a Canadian Consensus Statement; however, the patient's lived experience is that these guidelines aren't universally applied across Canada and across all Canadian treatment centres. Below are the main elements of thalassemia treatments:

1. Blood Transfusions:

- Regular blood transfusions are the cornerstone of treatment for TDT. These transfusions help to maintain a stable hemoglobin level and alleviate anemia-related symptoms.
- Transfusions are typically given every 1 to 5 weeks, depending on the individual's needs and the severity of their condition.
- However, frequent transfusions can lead to iron overload in the body, which can cause organ damage over time and eventually, lead to end organ failure and death if not removed.
- Treatment with blood transfusions alone will extend life expectancy from 5 years old (no transfusion) to early adulthood (death by heart failure at age 14 to 30 years old).

2. Chelation Therapy:
    - Chelation therapy is used to remove excess iron from the body and prevent iron overload.
    - Commonly used chelating agents include deferoxamine, deferiprone, and deferasirox. A main facet of TDT treatment for every patient is the use of at least one of these three chelator options. In some cases, two of these medications are used in combination.
        i. Deferoxamine, available since 1978, is administered subcutaneously via a 10 to 12 hour infusion using a battery operated pump. In cases of severe iron overload, deferoxamine may be administered intravenously over 24 hours a day, six to seven days a week through a portacath or a peripherally inserted central catheter (PICC) line similar to at-home chemotherapy treatments for oncology patients.
        ii. Deferiprone, available since 2015, is available in tablet form. Typically patients take up to 3 pills, 3 times a day. Recently, an extended-release (MR tablet) has been approved in Canada thus providing patients more flexibility; however, this version of deferiprone is not available in all provinces.
        iii. Deferasirox, available since 2007 as a dispersible tablet, is taken once a day by patients mixed as a slurry with water or juice. A tablet form was made available in 2016 and 3 or 4 tablets are taken once a day.
    - Chelation therapy is typically started once iron overload is detected, usually through regular monitoring of serum ferritin levels and iron concentrations in the heart and liver. Typically, iron chelation treatment begins in a TDT child between the ages of 2 and 5 years old.
    - Iron chelators have been proven to prevent or delay end organ damage.

- Adherence to these medications is considered to be life-saving for transfusion-dependent thalassemia patients. However, side effects such as itching, burning infusion sites or nausea/diarrhea make compliance to iron chelation medications a huge challenge.
- Iron chelation therapy extends and improves the life expectancy of TDT patients from early adulthood (approximately 14 to 30 years old) to later adulthood (60 years old and beyond).

3. Monitoring Parameters:
    - Serum Ferritin Levels: Serum ferritin levels are monitored regularly to assess iron overload. Elevated serum ferritin levels indicate excess iron in the body, which can lead to organ damage.
    - Liver MRI: Magnetic resonance imaging (MRI) of the liver is often used to assess iron overload in the liver, as excess iron can cause liver damage.
    - Heart Scans (MRI or Echocardiogram): TDT patients are at risk of heart complications due to iron overload, such as cardiomyopathy. Regular heart scans, either through MRI or echocardiogram, are used to monitor heart function and detect any abnormalities.
    - Bone Density assessments:TDT patients have a high prevalence of osteopenia or osteoporosis. Bone density assessments are done annually in TDT patients over the age of 30 years old to monitor for bone density loss.
    - Ophthalmologic Examinations: Regular eye examinations are important to monitor for complications such as retinal damage, which can occur as a result of taking iron chelation medication.
    - Audiologic Evaluations: TDT patients may undergo periodic audiologic evaluations to monitor for hearing loss, which can be associated with iron chelation treatments.

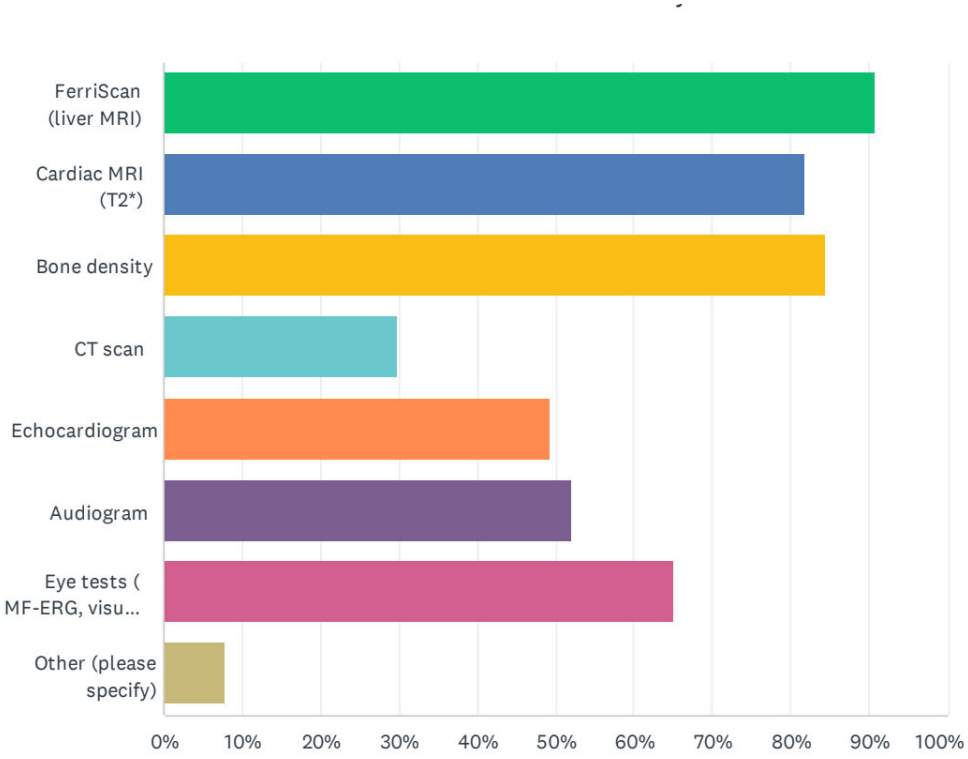

Figure 10. Tests patients receive

Other Supportive Measures:

- Luspatercept or Mitapivat: extends the time between transfusions and reduces the iron burden.
- Hydroxyurea: is used to reduce the effects of extramedullary hematopoiesis (EMH) and induces Hemoglobin F production in rare cases of thalassemia (Lepore syndrome).
- Folic Acid Supplementation: Folic acid supplementation is often prescribed to support red blood cell production.
- Nutritional Support: A balanced diet rich in iron-free foods is recommended to help maintain overall health and minimize iron overload.
- Vitamins or medication to maintain or restore bone density

Thalassemia patients and their caregivers face various challenges in managing the illness, but with currently available treatments, many are able to effectively control symptoms and improve quality of life and life expectancy. Below, we describe how well patients and caregivers are managing thalassemia with available treatments, along with associated benefits, side effects, and challenges:

Benefits Seen:

1. Blood Transfusions: Regular blood transfusions are highly effective in managing thalassemia major by alleviating symptoms of anemia and improving overall well-being. Patients often experience increased energy levels, reduced fatigue, and improved ability to participate in daily activities. Regular blood transfusions allow for normal growth and development along the lines of average children.
2. Chelation Therapy: Chelation therapy helps prevent iron overload, a common complication of frequent blood transfusions. By removing excess iron from the body, chelation therapy reduces the risk of organ damage and improves long-term outcomes for patients.
3. Supportive Measures: Nutritional support and folic acid supplementation help optimize red blood cell production and support overall health, contributing to better management of thalassemia symptoms.

Side Effects and Their Management:

1. Blood-borne pathogens and bacterial infections: Blood transfusions are beneficial to alleviating the symptoms and ill-effects of chronic severe anemia; however, patients remain vulnerable to transfusion-transmissible infections, known and unknown. Historically, the transfusion-dependent thalassemia patient population in Canada have been impacted by HIV and hepatitis C virus (HCV) infections. Implications of HIV and HCV in TDT patients include costly anti-viral treatments, loss of livelihood, and an increased risk of liver cancer or death. TDT treated in Canada before 1992 received tainted blood. Several patients succumbed to AIDS and about one-third of Canadian patients were infected with hepatitis C virus. Due to the combined assault on the liver by HCV and iron overload, many of these patients developed liver fibrosis, cirrhosis and some had liver cancer and died. HCV can be eradicated, and has, in a large number of TDT patients at a great financial and health cost. Current treatments cost around $77,000 for a short 8 week treatment. Many other patients tried earlier treatments which lasted 6 to 12 months and incapacitated them – they were unable to work, go to school and some side effects included aggression and other mental health issues. Other transfusion-transmissible infections such as West Nile Virus, Zika virus and Chagas disease are increasing in frequency in Canadian blood donors. The blood operators in Canada (Canadian Blood Services and HemaQuebec) ensure the quality and

safety of the blood supply at a cost borne by the provinces and territories. At the bedside, bacterial infection of Yersinia enterocolitica remains a risk of blood transfusion and is mitigated by best practices at blood collection, storage and transfusion steps.

2. Development of antibodies to donated blood: In Canada, this risk is lowered greatly by extended cross-matching of donated blood with that of the TDT patient; however, this level of cross-matching doesn't happen regularly in smaller hospitals or abroad. There is a growing number of young TDT patients in Canada who were transfused abroad, including in refugee camps. The level of thalassemia care abroad is inadequate compared to what is available in Canada. We are thrilled when patients have come to Canada from elsewhere but are alarmed at all of the health complications they face at such young ages. In young patients, many health complications such as iron overload can be corrected but the most basic of needs – blood transfusion – is hindered if the TDT child has many antibodies. Antibodies will make the TDT patient difficult to transfuse which will cause severe blood transfusion reactions (fever, rigours, hemolysis), prolonged anemia and discomfort and fear for the patient and their caregivers.

3. Iron Overload: Despite the benefits of blood transfusions, they can lead to iron overload, which will cause organ damage over time. Chelation therapy is used to mitigate this risk, but chelating agents themselves can have side effects such as gastrointestinal disturbances, joint pain, neutropenia, and kidney dysfunction.

4. Complications of Iron Chelation: Some patients may experience adverse effects from oral chelation therapy, such as allergic reactions, loss of immunity, kidney dysfunction. Desferal is known to cause bony growth abnormalities if doses are miscalculated or the iron load has lowered. Iron chelation can also cause hearing and vision loss. TDT patients are closely monitored to prevent complications or at least identify them before too much damage has occurred. Patients undergo a plethora of tests so doctors can follow their iron levels and all of the implicated organ systems (liver, vision, hearing, gastrointestinal, immunity, bone age and kidney function); these tests are done regularly via blood tests or diagnostic tests such as MRIs. Everything has to be monitored every year but due to accessibility and availability of some tests, this is not always done at the suggested frequency for each patient. If a test were to come back abnormal, a patient may have to undergo more tests, more medical appointments and hopefully get a swift intervention. There is always the risk of a patient's results being overlooked, forgotten or not followed up on promptly. As stated in Section 3, the multitude of specialists and tests can become a heavy burden on a TDT patient or caregiver. Within the complexity of TDT patient care some things get missed, or worse, a

patient falls through the cracks. With any well run machine, if one part breaks down then the whole machinery will stop functioning. If the TDT treatment and management machinery breaks down there could be a loss of life. Monitoring for these side effects and adjusting medication doses as needed is crucial for patient safety.

5. Treatment-related Fatigue: While blood transfusions improve energy levels for many patients, some may experience fatigue or weakness following the procedure.

Difficulties Accessing and Receiving Treatment:

1. Cost of Treatment: The cost of thalassemia treatments, including blood transfusions, chelation therapy, and supportive medications, can be significant. Access to affordable healthcare and insurance coverage for these treatments pose challenges for some patients and caregivers.
    a. Blood transfusions, always administered through hospitals, cost the provinces or territories approximately $1000 per transfusion visit per patient[1] (non-insured Canadian resident); in one year a patient's transfusions will cost their province or territory about $13,000.
    b. Unlike blood transfusion treatment, the cost of iron chelation is borne by the patient.
        i. Deferoxamine is covered by many provinces however this medicine is taken via daily needles or through portable intravenous access. In both cases, battery operated pumps cost patients between $1500 and $4000 because these pumps are not covered through hospitals, provincial plans or third party insurance. If home care is engaged to help a patient, these pumps are usually provided but then taken away when home care "discharges" a patient in a matter of months although the treatment is life-long and never ending. The supplies used to administer deferoxamine are no longer covered by hospitals, patients have to buy syringes, needles, tubing, dressings and medicine cassettes. Patients receiving deferoxamine via portacaths or PICC lines must have their medicine reconstituted under sterile conditions at a cost to the patient. Each of these steps takes careful coordination. For example, in Ottawa, a patient getting blood transfusions at the Civic Campus of the Ottawa Hospital must rely on a disjointed, multi-party approach to obtaining chelation therapy intravenously every week: deferoxamine is dispensed from the

[1] The cost for non-insured Canadian residents for one transfusion plus cross-match blood work cost $1037 in April 2024. The cost for International visitors for the same transfusion and blood work cost $3000 in March 2024 in an Ontario hospital..

Children's Hospital of Eastern Ontario at no cost and sent to Royal specialty pharmacy for reconstitution under sterile conditions and stored in a medicine cassette. The medicine in the cassette is delivered to the patient's home. The patient brings the medicine cassette to a third party specialty outpatient clinic (CBI Home Healthcare) where their PICC line will be cleaned and accessed by a nurse who will switch out the tubing and cassette into the battery-operated portable pump. This process is repeated weekly for 50 weeks. The patient pays $40 each week for the medicine cassette, dressing and reconstitution of the deferoxamine. On a monthly basis, IV deferoxamine patients must pay approximately $120 for additional supplies/services; while patients on subcutaneous deferoxamine must pay $552 that is not covered by social welfare programs for needles and tubing.

ii. The cost of deferiprone is close to $100,000 per patient per year.
iii. The cost of deferasirox is close to $54,000 annually (for brand name) or $15,000 (generic) per patient per year.
iv. Some patients are fortunate enough to have coverage through third-party private insurance; however, this coverage is often limited and can be denied once a patient has reached their lifetime coverage limit. For patients who do not have insurance coverage, they are relegated to seeking disability or other social welfare programs in order to pay for these medicines or the supplies required to administer deferoxamine.

"I worry about being able to retire because the cost of my medications are ridiculous."

2. Travel to Clinic: Thalassemia patients often need to travel to specialized treatment centres for blood transfusions and medical consultations. Travelling long distances to access care can be burdensome, especially for patients living in rural or remote areas.

   "Due to parking at the hospital being limited and a bit pricey, my wife now drops off/pickup for me every treatment. It takes up a bit of time from her work day."

3. Time Off School or Work: Regular medical appointments for blood transfusions, chelation therapy, and monitoring tests require patients and caregivers to take time off work, leading to potential financial strain and disruptions to daily life.

> “At least one day a month I am away from school and friends and one of my parents need to be absent from work unpaid.”

> “Jeopardizing my work. I take at approx. 12-14 days per year out of the 15 days vacation. I have other appointments too with CTs, doctors appointments, or being sick. All this is considered time off/no pay. At my work place, they don't allow us to work remote. Even during Covid.”

4. Disjointed access to health care: A patient’s health care has become disjointed and inefficient with each medical treatment being sectioned and administered through different delivery systems which means a patient must interact with more health care workers, take extra time and cost for travel, time off work, school or personal matters. For example, patients accessing specialized third party home care services for IV deferoxamine or luspatercept treatment must attend another clinic outside of their usual hospital transfusion visits which involves extra travel to third-party clinics on a weekly basis in addition to their regular transfusion clinic visits for this other necessary care. These patients also run the risk of breaks in communications and health records housed in multiple and separate locations.

5. Administration of Treatment: Some patients may struggle with the administration of treatment, such as swallowing pills or managing infusion lines for chelation therapy. Education and support from healthcare providers are essential to ensure proper administration and adherence to treatment regimens.

> “I feel that doctors and nurses that I meet yearly are very sensitive towards the condition. They are extremely helpful. I am really grateful for everyone. But a few nurses that I see in my regular transfusion dates are not sensitive to my condition, and sometimes it feels like we are a burden on the healthcare. it would be nice if the nurses that we see during transfusion are also sensitive towards the condition. I shouldn’t feel scared or unsafe while getting a transfusion or to ask basic questions.”

Estimating the lifelong costs of treating a thalassemia patient in the Canadian healthcare system involves considering various factors such as the frequency of required treatments, the cost of medications, and the management of complications

1. Blood Transfusions:
    - The cost of each blood transfusion session includes the processing and administration of blood products, as well as overhead costs associated with maintaining hospital

laboratories, blood banks and transfusion facilities; along with their equipment, supplies and human resources.
- Depending on the frequency of transfusions (typically every 2 to 4 weeks), annual costs can accumulate significantly, especially for a patient population treated from infancy and is now living into their 7th decade.
- Costs for patients/caregivers include travel to the transfusion appointment and missed work income.

2. Chelation Therapy:
    - The cost of chelating agents (e.g., deferoxamine, deferiprone, deferasirox) varies depending on the specific medication, dosage, and duration of treatment.
    - Chelation therapy requires regular monitoring of serum ferritin levels, iron concentration levels in the heart and liver; as well as other parameters, which may incur additional healthcare costs.
    - The high costs of iron chelation therapy is usually considered catastrophic and would be covered (to a maximum) by third party insurance or by provincial drug plans usually requiring the patient to seek a “disability” designation.

3. Supportive Medications and Nutritional Support:
    - Costs associated with supportive medications such as folic acid supplements and other vitamins may be considered and are typically out of pocket expenses for patients.
    - Nutritional support, including dietary counseling and specialized supplements, may incur additional expenses.

4. Monitoring Tests and Imaging Studies (see Figure 10):
    - Regular monitoring of serum ferritin levels, liver function tests, liver iron concentration assessments (FerriScan$^{(R)}$) cardiac assessments (T2* MRI and/or echocardiogram), bone density assessments, ophthalmologic evaluations, and audiologic assessments contribute to overall healthcare costs.
    - Imaging studies such as liver MRI (FerriScan$^{(R)}$) for assessing iron overload also add to the cost of care due to its proprietary licence.
    - These tests can be at a patient’s care centre, however the most specialized of these tests may require a patient to travel further to a specialty health care centre.

5. Complication Management:
    - Costs related to managing complications of thalassemia, such as infections, organ damage, and other medical conditions and interventions (e.g. emergency care), need to be taken into account.

6. Accessing Specialized Care:
    - Costs associated with accessing specialized thalassemia treatment centres, including travel expenses, accommodation, and time off work, may impact overall healthcare expenditures.

It's important to note that in Canada, healthcare costs are primarily covered by the public healthcare system administered at the provincial level. As such, the actual financial burden on patients and their families may vary depending on factors such as provincial healthcare policies, private insurance coverage, income levels, proximity to specialist care and eligibility for financial assistance programs.

Overall, while thalassemia patients and caregivers face various challenges in managing the illness, currently available treatments offer significant benefits in symptom control and improving quality of life. Close monitoring, individualized treatment plans, and comprehensive support are essential for optimizing outcomes and addressing the unique needs of each patient. Efforts to improve access to affordable healthcare and reduce barriers to treatment are crucial for enhancing the overall management of thalassemia.

Figure 11. Subcutaneous deferoxamine and supplies before reconstitution by patient

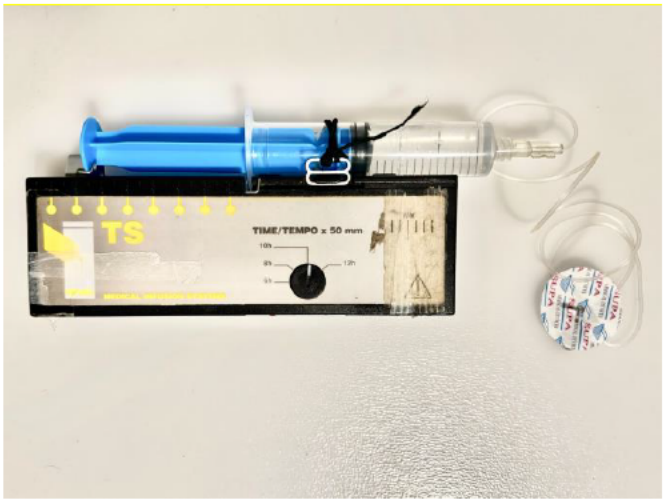

Figure 12. Reconstituted deferoxamine solution in syringe attached to pump for subcutaneous infusion;

Figure 13. Subcutaneous deferoxamine inserted in the patient's upper arm with pump bound to arm.

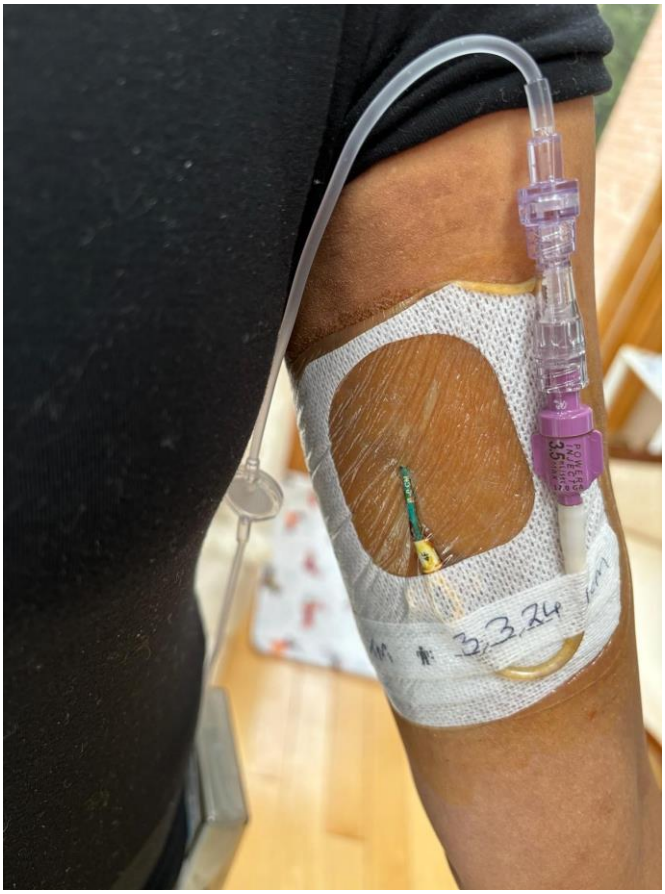

Figure 14. Image of a PICC line inserted in the upper arm for 24 hour deferoxamine IV infusion.

5. Improved Outcomes

Across all survey responses, the outcome most expected was removing the need to be dependent on transfusions, and the consequent improvement in quality of life. As discussed in sections prior, receiving transfusions, chelating, and the general stress of managing the disease places an immense burden on the patients.

> “What I expect is to receive fewer transfusions or none and to have few side effects from the gene therapy.”

A potentially curative treatment is the holy grail for thalassemia patients. If successful, it would significantly impact the quality of life on a daily basis. No more transfusions means less complications and time spent in hospitals, taking time off work and being away from family. It also means feeling healthier, participating in activities that they were unable to do because of their illness, and less money spent on the various treatment protocols and therapies outlined above. A potential cure would free patients from the ball and chain given to them at diagnosis and they would gain control over their own lives.

> “Better quality of life without so many appointments monitoring iron is kept at a safe level and no [damage has] been done to vital organs”

Patients were asked about their main expectations for gene therapy and the responses revealed the current burden patients live with:

Physical:

> “To not be blood transfusion dependant and have a better life quality”

> “For hemoglobin to maintain at a high enough level to function daily and reducing the need to go for blood transfusions by a significant time frame (every 6-12 months) or becoming completely transfusion independent.”

Systemic and Economic:

> “Similar to any other therapy. That it is accessible, efficacious, well researched, with a reasonable balance of risk to reward, and good support infrastructure post treatment.”

> “That it will be safe and effective and an option available to anyone who is a good candidate for it. Also, that it will be covered so that it’s accessible to everyone regardless of economic means.”

Psychological:

> “Being unbound from the chains of blood tubes and be able to work anywhere, travel anywhere and study anywhere. Not being stuck to a single city all my life. Not to mention the dramatic increase in my quality of life. Being able to express love without the fear of being treated as someone who is not partner material.”

As well as their hope for improvements to their quality of life with this new treatment:

> “I expect that gene therapy will allow my son to live a healthy life free of transfusions, it will allow his hemoglobin to be balanced which will remove the stress from his organs. It will allow his iron level to return to normal so that it will not harm his organs. It will free his time to spend with his friends and family and to pursue his career and allow him to travel.”

> “less visits to the hospitals/doctors. Less needles and medicine. More free time to enjoy with my family. More energy so I can work/earn more. basically a better quality of life in general”

Fundamentally, what the TDT patients and caregivers are expecting from this new treatment is to live like anyone else who doesn’t have thalassemia; free from the burden, pain and stress that is imposed on them every day. Freedom from the multitude of hospital visits, transfusions, medications, doctor appointments and diagnostic tests. A psychological unease will be lifted and people will gain greater control and not be controlled by the limitations of their bodies.

What trade-offs do patients, families, and caregivers consider when choosing therapy?

The trade-offs of this treatment include the unknown effects of preconditioning with chemotherapy drugs, including the risk of infection, infertility and death. There are also some assumptions that older TDT patients and/or those people with more medical complications or treatment side effects may face higher risks or that they will be deemed ineligible for this new treatment:

> “I expect that it may not be feasible for everyone. I hope that it can provide freedom from Thalassemia for everyone one day. I do worry about the difficulties such as chemo, pain and isolation surrounding this potential treatment.”

It is also recognized that this new treatment would reduce the complications and limitations of bone marrow transplants for TDT patients.

"... I would assume the ultimate goal is to eliminate the need for transfusions in a relatively safe manner to the health of the patient in contrast to the aftermath of a bone marrow transplant and the risks involved with older patients and imperfect matches."

"I was offered gene therapy years ago but quickly realized the risks out weighed the pros. I'd be interested if the treatment/recovery has improved since."

6. Experience With Drug Under Review

Below are stories shared by family members of patients treated by Vertex/CRISPR in the United States through clinical trials:

Patient 1:

" My daughter at age 13 underwent a stem cell transplant as part of the Vertex Crispr clinical trials in Nashville, Tennessee. Being cured of beta thalassemia major and the need for chronic blood transfusions and iron chelation medications, has been life changing for my daughter and our entire family. We are hopeful for the approval of this cure for our thalassemia friends around the world as being able to do it will be invaluable to them as well. One of the biggest things that can come from approval is that patients may be cured closer to home. Our travelling and being away from home for many months over the last years has added to the hardships of cure for our family. Also, a large advantage to approval for families will be that patients can undergo it at younger and younger ages and over time and avoid the complications that their bodies experience from the iron overload. My daughter now maintains a hemoglobin of 13+ all on her own and hasn't undergone a blood transfusion since 16 days post transplant! Please grant the thalassemia patients living in Canada the opportunity to be cured using this amazing technology by granting approval of Vertex Crispr."

Patient 2:

"Our son, participated in the Vertex CRISPR trial in November 2021.Life is so different for the entire family now! Medically, our son has not had any blood products since the week prior to admission. Our hospital/clinic visits have been limited to trial follow-up appointments and phlebotomy a small handful of times just after transplant. This is dramatically different from daily meds, double chelation therapy, specialist appointments, regular ER visits, nightly infusions, and the occasional emergency surgery- especially for our son, but those things also affected our family as a whole. His ferritin started at 15,000+ and is now in the normal range with no chelation. He's grown several inches, gained weight and confidence.
The bigger update is something that can't be measured by numbers and data. We hadn't realized how much anxiety he had "before" in relation to his illness and health, that he had

> actually been living in fear of dying. Before being adopted, our son's life expectancy in China was only 16 years old. He's 16 now and his life expectancy is.... unknown. Beautiful. Last weekend, he played his first flag football game. Finally, FINALLY, it was our son's turn to be part of the team. Not as a manager or a mascot or a kid with Thalassemia or recovering from chemo, not as the kid with a port. Just a regular kid.
> We couldn't be more grateful for the LIFE that CRISPR has given him, and us."

Furthermore, some patient respondents to our 2024 survey informed us they had considered or undergone either a stem cell transplant (involves preconditioning) or a gene therapy treatment via a clinical trial. Through the survey they were asked for their experiences:

> "My friend was in a Crisper trial which was ultimately unsuccessful and he almost lost his life"

> "Lots of work. Lots of chemo.lots of pain. Lots of recovery. Lots of time off. Lots of mental anguish after it didn't work.

> "I've already had a failed transplant. I would only go back if it was no chemo."

> "We had the Stem Cell transplant last September 2023, and it has been considered successful. It was a fantastic experience at Sick Kids, everyone was open, honest and helpful. We were discharged after +15 days after the transplant, stayed at Ronald McDonald House for 3 months and are home full time. After 6 months (post transplant) my son went to in person school, hasn't gotten sick, takes his meds, and is very happy to not have to take desferal/jadenu or have transfusions. Our appointments are now down to once a month and he is taking Sirolimus [anti-rejection drug] for the next few months."

> "I never went through with it because the thought of not having kids and having to freeze my eggs scared me but I did meet with the lead doctor a few times before I made my decision to not do it."

7. Companion Diagnostic Test

There are an assortment of specialized companion diagnostic tests necessary before the new treatment could be administered. By the nature of our chronic disease and dependence on specialized, hospital-based care for regular treatments, follow-ups and diagnostics (described in Sections #3 and #4), it is likely that some companion diagnostic tests for exagamglogene

autotemcel treatment will be similar and accessible in the same manner as they are for traditional treatment regimens for TDT patients. Below, the companion diagnostic tests are grouped in phases:

Pre-Consultation diagnostic tests (done by primary hematologist/referring physician):

1. Genotyping: this necessary to determine appropriateness of gene therapy
    a. Beta globin sequencing and alpha globin gene deletion/duplication
2. Liver iron concentration (LIC) and cardiac T2* (if >10yrs) within last 12 months
    a. Please note there will be a discussion with providers regarding if/when to repeat
    b. If there is a very high current iron burden, treatment may need to be deferred until iron is under better control.
3. Iron and transfusion history
    a. including transfusion frequency, chelation history and current ferritin/iron profile
        i. This includes transfusion records and blood bank records
4. Human leukocyte antigen (HLA) typing, if applicable

At transplant team visit:

1. HLA Antibody testing
2. Infectious disease marker labs (IDMs)
    a. HIV 1/HIV 2
    b. Hepatitis B Virus (HBV) core antibody/surface antigen
    c. HCV antibody
    d. Human T-lymphotropic virus (HTLV)-1/HTLV -2
3. Discuss hyper-transfusions to maintain hemoglobin (HGB) >/= to 110 g/L for at least 30 days prior to mobilization
4. Potential consent signing
5. Discuss fertility preservation options

Pre collection:

1. IDMs
2. Within 30 days of mobilization
    a. HIV 1/HIV 2
    b. HBV core antibody/surface antigen
    c. HCV antibody
    d. HTLV-1/HTLV -2
3. Maintain HGB >/= to 110 g/L for at least 30 days prior to mobilization
4. Stop anti-retroviral for at least 30 days prior to mobilization

5. Stop hydroxyurea 30 days, if applicable

Pre-transplant workup:

1. Maintain HGB >/= to 110 g/L for at least 30 days prior to transplant
2. Pre-transplant labs
3. Chest CT
4. Pulmonary function tests (PFTs)
5. Echocardiogram (ECG)
6. Evaluation of both cardiac and liver iron loading, performed by a Cardiac T2* MRI and a Liver R2*, ferriscan, or T2* MRI will be necessary.
7. Stop iron chelation at least 7 days prior to admission
8. Pre-transplant education

Across Canada, although blood transfusions can be obtained in most hospitals, it is very well known that specialized hospital centres such as pediatric hospitals and/or adult teaching hospitals have the variety of specialists (hematology, endocrinology, cardiac, ophthalmology) and specialized diagnostic tests (T2* Cardiac MRI, FerriScan (liver MRI), etc. as described in Section #4) that are required for the complex and comprehensive care required for transfusion-dependent beta-thalassemia patients (Consensus Statement on the Clinical Care of Patients with Thalassemia in Canada). Access to these comprehensive treatment centres varies depending on the location of individual patients.

It is our understanding that this new treatment requires a patient to undergo myeloablation or myeloablative conditioning regimen. This sort of conditioning can only be done in specialized transplant centres and as such patients and their caregiver(s) will be required to travel to a transplant centre which may be different than their usual comprehensive treatment centre. It is our understanding that not every transplant centre would host patients undergoing treatment with exagamglogene autotemcel; rather patients may need to travel to a larger city within or outside of their home province in order to obtain this novel treatment.

8. Anything Else?

This new treatment, exagamglogene autotemcel, is not an off-the-shelf, one-size-fits-all drug. Rather it is a highly invasive treatment with the potential to materially affect a patient's life. It involves removing a patient’s stem cells, then treating the stem cells in a laboratory and then infusing the gene-edited stem cells back into the patient who has awaited this treatment while in hospital undergoing chemotherapy to extricate all of their own defective bone marrow. This treatment will be customized for each individual TDT patient and represents a new era in treatment

for a chronic genetic disease. Yet, TFC is submitting this form for a “new drug” which indicates that there does not seem to be a system or process in place to assess customized gene-editing treatments that will result in an unique product for each individual patient. If the form is the same used for a new drug then we also assume that the assessment tools used by CADTH may have been designed for a “new drug”. We respectfully request that the assessment be flexible enough given that this treatment in some ways may not fit the standards used to assess new drugs. If there is a greater parallel in the oncology treatment world then this review should possibly follow those. The level of intervention and specialized in-hospital care that is required for one patient makes this “new drug” seem more like an oncology treatment, like chimeric antigen receptor (CAR)-T cell therapy.

We asked respondents if gene therapy could be available in one to two years, do they have any concerns? Respondents could identify as many concerns as they wanted to. Patients and caregivers responded with concerns around cost and affordability of treatment (75%), length of treatment/recovery (71%), chemotherapy (61%), as well as eligibility due to older age.

50 years ago children diagnosed with TDT had little to no hope of living to the age of 20. Every new treatment has given patients and their families/caregivers hope that life could be longer and better and “normal”. But every treatment has its costs – financial, physical and psychological side effects that make access and compliance difficult. Availability, accessibility and affordability are three tenets that were repetitively noted in the survey responses. They must constantly be upheld in order to provide timely, affordable and safe care to patients, but many therapies today see disruption to one of these pillars. Drug shortages, cost markups and lack of adequate insurance coverage and general lack of knowledge of healthcare providers outside of major treatment centres allows for patients to fall through the cracks, often with dire consequences.

For these reasons patients are interested in new treatments and have hope for better options. Adding this new treatment for TDT to the arsenal of options will lessen the burden for a portion of Canadian TDT patients. Exagamglogene autotemcel treatment won’t be a panacea for all patients but it will be an option to help people. For example, this treatment could be an option for TDT patients who are the most difficult to transfuse -- patients with auto-immune hemolytic anemia or with antibodies. The treatment may also be ideal for young TDT patients with few long-term complications which will relieve them of the decades-long burden of accessing constant specialty care in an overtaxed health care system.

Our patient group has endured a lot. For these individuals, the sense of having no control over their own lives is utterly demoralising. The psychological trauma from being constantly vigilant and expecting the worst often compounds with the physical effect of thalassemia. For those who have lived– and continue to live– with this onerous disease deserve to have access to safe, effective

treatments. Approval of this curative therapy is just another stepping stone towards improved care for this patient population in Canada.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, 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 Thalassemia Foundation of Canada struck a working group in order to plan and prepare this submission. The working group was composed of Board members and volunteers from the thalassemia community.

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, the Thalassemia Foundation of Canada struck a working group in order to prepare a survey for patients and caregivers to inform this submission. The working group was comprised of Board members and volunteers from our community.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 2: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
nil	0	0	0	0

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: Bessie Calabria
Position: President
Patient Group: Thalassemia Foundation of Canada
Date: May 13, 2024

Clinician Group Input

CADTH Project Number: SG0831-000

Generic Drug Name (Brand Name): exagamglogene autotemcel

Indication: Transfusion-dependent β-thalassemia

Name of Clinician Group: Canadian Hemoglobinopathy Association (CanHaem)

Author of Submission: Catherine Corriveau-Bourque

1. About Your Clinician Group

The Canadian Hemoglobinopathy Association/ L'Association canadienne d'hémoglobinopathie (CanHaem) is a not for profit organization that was established in 2013 and is composed of healthcare providers dedicated to the care of individuals in Canada with hemoglobinopathies. CanHaem aims to provide multidisciplinary expertise and advance the quality of care to patients across the country through education, research, and advocacy in collaboration with key partners.

https://www.canhaem.org/

2. Information Gathering

This submission was drafted by the CanHaem chair and shared with other members for review. Information for this submission was gathered from our clinical practice and expertise, perspectives from patients and families in clinic, published national and international guidelines on the management of transfusion dependent thalassemia (TDT), as well as a review of published literature.

3. Current Treatments and Treatment Goals

Thalassemias are a heterogeneous group of disorders resulting from defects in hemoglobin production. Migration patterns are such that the number of people affected with thalassemias in Canada has substantially increased over time.

Transfusion dependent beta thalassemia (TDT) is a severe, autosomal recessive disorder due to pathogenic variants in the beta globin gene, HBB, resulting in absent or greatly reduced beta globin production and consequent ineffective erythropoiesis and chronic hemolysis.

Patients with thalassemia require subspecialty multidisciplinary care throughout their lives. Standard of care for patients with TDT in Canada includes lifelong transfusions with red blood cells approximately every 3-4 weeks. The transfused red cells contain iron, which cannot be excreted naturally resulting in iron overload. Patients require lifelong daily iron chelation therapy in order to minimize the risk of potentially life-threatening end organ damage.Iron overload leads to dysfunction of the heart, liver, and endocrine tissues resulting in complications such as arrhythmias and heart failure, liver fibrosis and cirrhosis, as well as insulin dependent diabetes and hypopituitarism. Additional complications of thalassemia include but are not limited to pulmonary hypertension, venous thromboembolic events, and extramedullary hematopoiesis (EMH) which can cause hepatosplenomegaly and axial skeleton pseudotumors that may lead to complications including paralysis. The treatment goal for TDT patients is transfusion therapy to sustain life, normal growth and development as well as reduce the complications of the disease process, in addition to reducing the iron burden through iron chelation therapy. Patients with thalassemia experience poor health related quality of life (HRQoL) compared to the general population and health care related costs are estimated to be 140,000 USD per patient per year, which is mainly derived from the high cost of iron chelation.

Currently, iron chelation therapy options include oral agents deferasirox and deferiprone as well as subcutaneous or intravenous deferoxamine, either used as single agents or employed as dual chelation therapy in patients with dose limiting toxicities or severe iron overload.

Luspatercept, is now approved for use in TDT patients 18 years of age or greater in Canada. It is an erythroid maturation agent that can reduce the transfusion burden by one third in approximately 20% of transfusion dependent beta thalassemia patients. Despite only a modest reduction of transfusion burden, luspatercept is associated with an improvement in quality of life amongst responders highlighting the burden that chronic transfusions place on patients with thalassemia. Unfortunately, the majority of TDT patients do not respond to luspatercept and post-marketing surveillance has identified paraspinal EMH as complication limiting therapy in some patients.

In patients seeking curative therapy, hematopoietic stem cell transplant (HSCT) can be considered for pediatric patients with an HLA matched sibling donor (MSD), and do not have evidence of hepatic fibrosis or significant hepatic iron overload. Only 10-15% of patients will have a MSD and the optimal age for transplant is less than 14 years of age. With MSD HSCTs, overall and disease free survival ranges 80 to >90%, chronic graft versus host disease (cGVHD) 5-12% and are associated with significant morbidity. Additional challenges in this population are 1) the increased risk for graft failure as compared to other populations undergoing transplant due to the ineffective erythropoiesis with increased erythroid expansion as well as prior sensitization to RBC antigens and HLA from a lifetime of transfusions 2) the increased risk for veno-occlusive disease related to prior liver iron damage. HSCT with alternative donors (matched unrelated or haploidentical donors) may be performed but the treatment free survival is inferior compared to MSD transplants, and is therefore not standard of care.

The curative gene modifying therapy Betibeglogene autotemcel, produced by Bluebird Bio has been approved by the FDA and the EMA, but was withdrawn from the European market due to failure of price negotiations. We understand that the company does not intend to market this product in Canada, and there are no other commercially available gene therapy products.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

With improvement in transfusion safety, monitoring for iron overload and chelation patients with thalassemia may have near normal life expectancy. However, emerging disease-related complications are now appreciated in the aging thalassemia population including increased risk of hepatocellular carcinoma, as well as renal, cardiac and hepatic failure, all of which are related to the chronic toxicity of iron.

The impact of this chronic disorder on health-related quality of life (HRQoL) as well as increased risk for mental health issues like anxiety and depression is well described. Comparing HRQoL inventory responses in patients with TDT and controls reveals lower subscores in all areas of functioning. Anxiety and depression in TDT patients have been reported at rates similar to those of other severe chronic health conditions like cystic fibrosis and diabetes. Mental health issues negatively impact adherence to medication and overall health status.

Lifetime cost estimates for patients with transfusion dependent beta thalassemia range $500,000-7 million USD, the bulk of the costs being attributed to iron chelation therapy and chronic red blood cell transfusions. Some of the variability includes estimated life expectancy and management of complications. The financial burden on patients and families as a result of medication insurance, cost of supplies for patients requiring subcutaneous iron chelation infusions, and indirect health care related costs including transportation, child care and time away from work and school for transfusions and other health maintenance appointments. Intangible costs including patient and family suffering related to the diagnosis, and loss of economic opportunity are difficult to quantify.

There are multiple other challenges with standard of care for TDT. In addition to iron overload, long term red blood cell transfusions can result in alloimmunization, which can make obtaining blood challenging,and placing strain on Canadian Blood Services and HemaQuebec resources. Furthermore, iron chelation therapy has the potential for significant side effects and dose-limiting toxicities, including renal failure, that further contribute to poor HRQoL and non-adherence to chelation therapy that may result in life-threatening acute complications including hepatic and cardiac failure resulting in high acute care utilization costs.

Given the significant burden of disease, curative therapies are frequently requested by patients and families. However, the minority of patients (<20%) have an unaffected, eligible, MSD donor. Alternative donor transplants may be considered in some patients although HSCT with alternative donors are performed but the outcomes are inferior to MSD transplants. There are new conditioning regimens showing promise in terms of rates of overall survival, disease free survival and even cGVHD; however, the longer term outcomes of these regimens have yet to be determined.

The side effect profile of any HSCT may be unacceptable to some families, particularly the risk for infertility. Fertility preservation is important for many families; however, optimal transplant timing is prior to an age where fertility preservation is an option for some patients.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Exagamglogene autotemcel (exa-cel) represents a significant shift in the current treatment landscape by providing highly efficacious, one-time disease modifying therapy, in contrast to decades of transfusion and iron chelation. Notably, two Canadian centers participated in the thalassemia arm of the phase III exa-cel trial and Canadian patients have had the opportunity to experience the freedom from transfusions, chelation and improvement in quality of life that this therapy brings.

Exa-cel targets the erythroid-specific enhancer region of *BCL11A* in hematopoietic stem and progenitor cells via (CRISPR)–Cas9 gene editing to reactivate fetal hemoglobin synthesis. The goal of exa-cel in TDT patients is to increase fetal hemoglobin production sufficiently to eliminate the need for chronic transfusion therapy and eventually, iron chelation therapy. In the recent New England Journal of Medicine publication, 91% of patients met the primary endpoint of transfusion independence for at least 12 consecutive months. In addition, 91% met the secondary endpoint of an average hemoglobin level of at least 90g/L without red blood cell transfusion for at least 6 months, with red cell transfusion independence at a mean of 35.2 days after exa-cel infusion. Those patients who achieved transfusion independence have remained transfusion independent through the follow-up period. Of those who did not initially achieve transfusion independence, one had a significant (84%) decrease in red cell transfusion volume and the two others later were able to discontinue red blood cell transfusions.

The majority of side effects experienced by patients in the trial were in keeping with known busulfan side effects, including myelosuppression, febrile neutropenia, and mucositis. There were some severe adverse events reported in patients who received exa-cel; however, most were also attributed to the busulfan conditioning regimen and are well described with busulfan use in the transplant setting. SAEs included veno-occlusive liver disease, acute respiratory distress syndrome and idiopathic pneumonia syndrome in the context of hemophagocytic lymphohistiocytosis, intracranial bleed, and delayed engraftment. To date, no deaths or cancers have occurred post exa-cel infusion. No off-target site editing has been detected in the assessments performed to date and there are no reports of therapy-related malignancy thus far..

Significant advantages of this therapy are that, unlike allogeneic HSCT, 1) there is no risk for acute or chronic graft versus host disease, 2) there is no exposure to stem cell donor HLA and RBC antigens.

To date, transfusion independence has been durable; however, at this time, there is no long term data available for exa-cel use with the longest follow-up reported at 48.1 months. Therefore, until longer term data is available, we anticipate that this therapy be used in patients seeking a curative option but are ineligible for MSD HSCT. Eliminating the need for red blood cell transfusions and eventually iron chelation therapy would be life changing for patients.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Potentially eligible TDT patients would be identified by their hemoglobinopathy team. At this time, we believe TDT patients could be offered exagamglogene autotemcel if they do not have an available HLA-matched sibling donor, meet age requirements (currently 12-35 yo but there is an ongoing clinical trial for lower age group) and are otherwise felt to be eligible for this therapy. We note that the FDA did not cite an upper age limit for receipt of this therapy and we believe that age >35 years should not be an absolute exclusion criteria. In addition, patients up to 50 years were included in the betibeglogene autotemcel trial. Patients are likely to experience less toxicity with a lower iron burden and efforts to optimize chelation, if possible, would be suggested.
Exclusion criteria would be similar to those in the study, including advanced liver disease, cardiac MR T2 <10ms or left ventricular ejection fraction < 45%, baseline estimated glomerular filtration rate < 60 mL/min/1.73 m2, diffusing capacity of the lungs for carbon monoxide (DLco) <50% of predicted (corrected for hemoglobin and/or alveolar volume). CanHaem is committed to ensuring that there is national equity to patients receiving this life-altering therapy and will work to develop national access strategies for patients across the country.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Outcomes used to determine response would include the same endpoints as the clinical trial: transfusion reduction or independence increase in total hemoglobin, decrease in serum ferritin and tissue specific iron overload, and discontinuation of chelation over time. In addition, HRQoL outcomes should be monitored in alignment with clinical trials.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Not applicable as this therapy is only performed once

5.5 What settings are appropriate for treatment with drug under review? Is a specialist required to diagnose, treat, and monitor patients who might receive drug under review?

Hemoglobinopathy providers from established adult and pediatric centres would identify potentially eligible patients. Treatment with exagamglogene autotemcel would ideally occur at a facility experienced with stem cell collection, administration of myeloablative chemotherapy and specialized hematologic care. Patients will need to be admitted to hospital for approximately 35 days to facilitate neutrophil engraftment. Patients will require long-term follow-up from their hemoglobinopathy providers to ensure there are no long-term complications of thalassemia, iron overload, conditioning chemotherapy and the exa-cel product, in addition to follow-up from their transplant center.

6. Additional Information

CanHaem would like to highlight the need for equitable access for this therapy to eligible patients, so that patients, regardless of their geographic distance from treatment centers are able to access this therapy. In addition, CanHaem recognizes that this treatment is associated with a high risk of infertility and that the cost of fertility preservation should be included in price negotiations.

7. Conflict of Interest Declarations

CADTH

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

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

   No

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

   No

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. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

CanHaem – the following companies provided sponsorship of our annual meeting in 2022 and 2023

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Vertex				x
Chiesi				x
BMS				x
Pfizer		x		
Alexion		x		

Declaration for Clinician 1

Name: Catherine Corriveau-Bourque

Position: Pediatric Hematologist

Date: 08/05/2024

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

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Vertex	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Hayley Merkeley
Position:Adult Hematologist
Date: 09/05/2024

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

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Vertex Pharmaceuticals	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Lauren Bolster

Position: Adult hematologist

Date: 13-05-2024

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

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Vertex Pharmaceuticals	x			

* Place an X in the appropriate dollar range cells for each company.

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