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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/system/files/coi_form_ebk.pdf
https://yoda.yale.edu/system/files/coi_form_sb.pdf
https://yoda.yale.edu/system/files/coi_form_fp.pdf
https://yoda.yale.edu/system/files/coi_form_js_0.pdf

Certification

Certification: All information is complete; I (Pl) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. AC-056C501 - NPC Registry (AC-056C501) Registry is an international, multi-center, prospective, observational, long-term project for patients diagnosed with NP-C
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Intrathecal Adrabetadex for Niemann-Pick Type C (NPC): Case Control Study in Early Onset NPC and Comparison of Natural History and Treated Cohorts

Narrative Summary:

NPC is a heterogenous fatal neurogenerative disease due to impaired cholesterol trafficking. A phase 1/2a trial of adrabetadex showed cholesterol efflux from brain, normalization of biomarkers, and slowing of disease progression. A phase 2/3 1-year sham-controlled trial showed no benefit, as the sham group had little progression. In the proposed study, data from this dataset and other natural history cohorts will be used to 1) match patients with early onset disease treated with adrabetadex in expanded access to historical controls and evaluate long-term outcomes of survival and loss of ambulation; 2) compare progression of disease combined cohorts of all treated and untreated patients.

Scientific Abstract:

Background: Niemann Pick type C is a heterogeneous fatal neurodegenerative disease resulting from mutations in NPC1 or NPC2, with resultant impaired cholesterol trafficking and cholesterol accumulation in the lysosomes and late endosomes. Adrabetadex showed benefit in NPC cats and mice, with substantial prolongation of life, slower motor decline, and rescue of cerebellar Purkinje cells. A phase 1/2a trial of adrabetadex showed cholesterol efflux from the brain, normalization of biomarkers of neurodegeneration in CSF, and slowing of disease progression. A phase 2b/3 one year sham controlled trial failed to show benefit as the sham group had little progression. Patients with early onset disease under age 5 not eligible for the trial have been treated through an Expanded Access Program (EAP) and many seem to be showing strong responses with no progression over years and ongoing developmental gains. When patient groups treated long-term through both EAP or open-label extensions of trials are combined and compared to a natural history cohort, the treated patients show a slower rate of progression. Objectives: To determine 1) if early onset patients with NPC treated with adrabetadex show improved survival and delay in loss of ambulation relative to matched untreated patients and 2) if patient cohorts treated long-term with adrabetadex progress more slowly than natural history controls. Study Design: Each patient with disease onset under age 5 years who has been treated with adrabetadex will be matched to as many historical controls as possible from this database and other sources, based on developmental milestones and clinical features and will be compared with respect to age of loss of ambulation and death, as well as other secondary outcomes to be determined based on data available. Data from all adrabetadex-treated patients from both EAP and trials as well as natural history controls from multiple cohorts including this dataset will be compared with respect to time to progression and overall survival. Participants: All patients treated with adrabetadex through EAP or trials and natural history controls from this and other existing databases. Main Outcome measures: age of death and age of loss of independent ambulation for matched case-control study of treated/untreated patients with early onset disease; time to progression and overall survival for treated and control cohorts of all patients. Statistical Analysis: Kaplan-Meier methodology and other methods.

Brief Project Background and Statement of Project Significance:

Niemann Pick type C is an ultra-rare heterogeneous fatal neurodegenerative disease resulting from mutations in NPC1 or NPC2, with resultant impaired cholesterol trafficking and cholesterol accumulation in the lysosomes/late endosomes (1,2). Adrabetadex showed benefit in NPC cats and mice, with substantial prolongation of life in mice (3,4) and cats (5), slowing motor of decline and rescue of cerebellar Purkinje cells in cats (5). A phase 1/2a trial of intrathecal adrabetadex showed cholesterol efflux from the brain after infusions, normalization of biomarkers of neurodegeneration in CSF, and slowing of disease progression over 18 months relative to matched natural history controls (6). A phase 2b/3 one year sham controlled trial failed to show benefit as the sham group had little progression (7). Some patients treated through an Expanded Access Program (EAP) seem to show an excellent
response (8), particularly those with early onset under age 5, who were not eligible for trials, and have had no progression in years and ongoing developmental gains (9). When patient groups treated long-term through EAP or open-label extensions or trials are combined the treated patients show a slower rate of progression compared to a natural history cohort (10) and reduction of progression slope in individual patients compared pre- and post-treatment (11,12). In NPC, placebo/sham-controlled trials are highly challenging due to variability of the disease (1,13), slow progression over years, and limited numbers of patients. Any trial must be small and cannot be stratified by many variables due to cohort size. Thus, there is high risk of randomizing a group to the control arm which is progressing at a different rate than the treated arm, especially when the control arm is smaller based on a 2:1 randomization scheme often employed to try to limit the number of patients subjected to loss of skills while in the control arm. This is further complicated, in NPC, by the use of miglustat, which slows the natural disease course (14-18), by a substantial proportion of patients. The phase 2b/3 trial of adrabatedex in NPC was subject to all these issues and the control group failed to progress at a rate that would allow a definitive determination of drug effect for adrabatedex (7). The only way to truly understand the drug effect in this situation is to look at long-term data and compare treated cohorts with available natural history cohorts, look at within patient pre- and post-treatment rates of decline, and use case-control designs to study very young children who were not a part of the phase 2b/3 trial and who have the fastest rate of progression, thus allowing for the shortest treatment time to pass before outcomes like survival can be assessed. In this study, we will use information from the YODA NPC registry to add to the pool of control patients that can be used for case-control and natural history comparator studies to show a long-term effect of adrabatedex that will, if a sufficiently strong result, contribute to a registration application by Mandos for accelerated approval at FDA. If this project is successful it will help make available an important treatment for NPC.

Specific Aims of the Project:

Specific Aim 1: To show decreased longer survival and longer time to loss of ambulation in children with NPC and neurological onset at <5 years treated with adrabatedex relative to matched natural history controls in a case-control design. 
Hypothesis: Adarbatedex-treated children with early onset NPC will show longer survival and a longer time to loss of ambulation, relative to matched controls.
Specific Aim 2: To show longer time to progression and increased overall survival in entire treated cohort compared to combined natural history cohorts.
Hypotheses: 1) Adrabatedex-treated patients will show longer time to progression and increased overall survival relative to the natural history controls; 2) Time to progression will be more prolonged by adrabatedex in patients early in disease and in younger patients.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
Research on comparison group

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Aim 1 data sources for this study will include 1) data from adrabatedex-treated patients in RedCap and excel files housed at Rush University Medical Center (RUMC), data from untreated controls from 2) this YODA NPC registry, 3) the International Niemann-Pick Disease Registry (19), 4) databases for NPC cohorts in France from Marie Vanier (1) and Germany by Heiko Rutz (20) the NIH natural history study in the NIH CTDB database, and 6) the Allstripes NPC database. For Aim 2 data sources will include the above and the Mallinckrodt trial/EAP databases (21) : VTS301 (phase 2b/3), VTS302, VTS001 and OLEX.
Aim 1 inclusion criteria will be children with NPC treated with adrabatedex prior to age 5 years due to neurological symptom onset under age 5 years and untreated matched controls from all sources. Matching criteria will be developmental milestones and neurological symptoms at the age of treatment initiation for each treated patient. Aim 2 inclusion criteria will be all adrabatedex treated patients from all sources and controls from all sources. Patients will be excluded from both Aims if they have medical complications or additional diagnoses that would impact the course of NPC.

Main Outcome Measure and how it will be categorized/defined for your study:
For Aim 1 the main outcomes will be 1) age of death defined as death from any cause; 2) age of loss of ambulation defined as inability to ambulate independently without a support device or assistance, after having previously ambulated independently. Depending on specific data available in the databases, time to progression may be utilized for this Aim, defined as time to worsening of an existing neurological symptom or appearance of a new neurological symptom (potential symptoms (1,2) would include ataxia, dystonia, dysarthria, dysphagia, dysmetria and cognitive decline (22,23)).

For Aim 2 the main outcomes would be 1) age of death defined as death from any cause; 2) time to progression defined as worsening of at least 2 points on the NPC Severity Scale (NPC-SS) 5 Domain Scale (24,25) and/or (depending on data available) time to worsening of an existing neurological symptom or appearance of a new neurological symptom (potential symptoms would include ataxia, dystonia, dysarthria, dysphagia, dysmetria and cognitive decline).

Main Predictor/Independent Variable and how it will be categorized/defined for your study: For both Aim 1 and Aim 2 the main predictor/independent variable will be treatment with intrathecal adrabetadex continuously for at least one year.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Other variables of interest that will need to be accounted or controlled for in both Aim 1 and Aim 2 are:
1) use of miglustat defined as continuous use for the majority of the follow up period to be analyzed for the patient
2) severity of disease at initiation of adrabetadex treatment defined as severity of gross motor/ambulation and speech delay (23) for Aim 1 (this will be accounted for in the matching in Aim 1) and defined as NPC-SS 5 Domain score (25) for Aim 2
3) rate of progression at initiation of adrabetadex treatment Annual Severity Increment Score (ASIS) (11) based on the NPC-SS 5 Domain score
4) age at initiation of treatment

Other variables that may be of interest include:
1) NPC1 mutation (20)
2) biomarker measures to be determined, but potentially including 24-OH-cholesterol release post-infusion, calbindin D, fatty acid binding protein 3 (6), bile acid B or other lipid metabolites (26,27) and potential new biomarker of treatment effect, GPNMB (28)

Statistical Analysis Plan:

General Data Analyses Conventions:
Each patient with disease onset under age 5 years who has been treated with Adrabetadex will be matched to as many historical controls as possible from these databases, based on developmental milestones and clinical features and will be compared with respect to age of loss of ambulation and death, as well as other secondary outcomes to be determined based on data available.

All planned statistical analyses are exploratory. No sample size will be calculated, and no minimum sample size was determined a priori. Unless otherwise stated, descriptive statistics will be used to summarize continuous variables; categorical variables will be summarized using the total number of available values and the number of available values in each category.

The data from various databases will be pooled to form an overall pooled data set. Duplicate records for patients who were included in both the NPC Registry and one of the studies will be identified programmatically and the information censored as needed. The overall survival OS is defined as the time from the study entry or randomization to death from any cause. For patients who are alive at the time of the analysis data cutoff, OS time will be censored at the last date the patient was known to be alive or analysis data cutoff date, whichever occurs first. Patients with no post baseline survival information will be censored on the date of study entry or randomization.

Statistical Analyses for Aim1:
The Primary survival analyses will be performed using an extended Cox model, which will include treatment (adrabetadex-treated vs untreated), category of age at onset of neurological manifestations and country (each country in the NPC Registry and the national cohorts) as covariates. For treatment comparisons, adjusted Kaplan Meier (KM) curves, adjusted hazard ratios (HR), the 95% confidence intervals (CI) and P-values will be calculated.
as needed.

For Aim 1 the date of loss of ambulation defined as the date when the patient is unable to walk independently without a support device or assistance, after having previously ambulated independently. Depending on specific data available in the databases, time to progression may be utilized for this aim, defined as time to worsening of an existing neurological symptom or appearance of a new neurological symptom (potential symptoms (1,2) would include ataxia, dystonia, dysarthria, dysphagia, dysmetria and cognitive decline (22,23)).

Time to loss of ambulation and/or time to progression will be analyzed using an extended Cox model, which included treatment (adrabetadex-treated vs untreated), category of age at onset of neurological manifestations, and country (each country in the NPC Registry and the national cohorts) as covariates. For treatment comparison, adjusted Kaplan Meier (KM) curves, adjusted hazard ratios (HR), the 95% confidence intervals (CI) and P-values will be calculated as needed.

Statistical Analyses for Aim2:
For Aim 2, the Overall survival analyses will follow the same definition and analyses except the extended cox model will adjust for treatment and country (each country in the NPC Registry and the national cohorts) as covariates only.

The time to progression defined as worsening of at least 2 points on the NPC Severity Scale (NPC-SS) 5 Domain Scale (24,25) and/or (depending on data available) time to worsening of an existing neurological symptom or appearance of a new neurological symptom (potential symptoms would include ataxia, dystonia, dysarthria, dysphagia, dysmetria and cognitive decline). The time to progression will follow the same analyses as in aim1 except the extended cox model will adjust for the treatment (adrabetadex-treated vs untreated) and country (each country in the NPC Registry and the national cohorts) as covariates only.

Miglustat use status (yes/no) will be used as an additional covariate in the extended cox model for the sensitivity analysis purpose

Software Used:
R

Project Timeline:

In this project data must be obtained from multiple sources and so this has resulted in delays. The Mallinckrodt databases were locked in December 2021 but other data sources are not yet available. It is hoped that these can become available by December 2022, matching for the case-control study completed by March 2023, and complete data analyses completed by December 2023. The timeline for Aim 1 could be delayed if data from other sources continues to take longer than expected to obtain. Once data is analyzed this would, depending on results, be used by Mandos to submit an NDA to FDA by December 2023 and then publish data while working with FDA on the response, such that publication would be expected in the second quarter of 2024. Results could be reported back to the YODA project shortly thereafter.

Dissemination Plan:

Results of these studies will be published in peer-reviewed journals. Appropriate journals would be those read by neurologists and geneticists including Neurology, Annals of Neurology, Pediatric Neurology, Science Translational Medicine and multiple others. Results would be presented at relevant national conferences including the Child Neurology Society, WORLD, American Society of Medical Genetics meetings, as well as meetings of disease stakeholders, including but not limited to the Ara Parseghian Medical Research Foundation, the National Niemann-Pick Disease Foundation, and the Niemann-Pick UK meetings.

Bibliography:

1. Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis 2010;5:16.
2. Berry-Kravis E. Niemann-Pick Disease, Type C: Diagnosis, Management and Disease-Targeted Therapies in Development. Semin Pediatr Neurol. 2021 Apr;37:100879.


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Supplementary Material:

https://yoda.yale.edu/sites/default/files/yoda_project_research_proposal_direct_data_access_16-09-29_for_npc_ebk.pdf