ORIGINAL ARTICLE

Infantile Spasms and Trisomy 21: Unfavorable Outcomes with First-line Vigabatrin Therapy

Anita N. Datta, Jacqueline Crawford, Peter K.H. Wong

ABSTRACT: ***Introduction:*** Among children with infantile spasms (ISs), those with trisomy 21 (T21) and those with normal development at onset and no identifiable etiology (previously referred to as "idiopathic") are expected to have relatively favorable outcomes. The study objective is to determine if differences exist in treatment response, relapse, and subsequent epilepsy between these two groups when vigabatrin is used as first-line treatment. ***Methods:*** In this retrospective study, patients were classified into the following groups and clinical features were compared: T21 (n = 24) and IS with normal development at onset and no identified etiology (n = 40; control group). ***Results:*** There was no significant difference in the age of IS onset, sex distribution, or treatment lag between the groups. The T21 compared to the control group required a higher mean number of anti-seizure therapies (3.6 vs. 1.9, $p < 0.001$), had more relapses [10 (42%) vs. 4 (10%), $p < 0.005$)], and had higher risk of subsequent epilepsy [11 (46%) vs. 8 (20%), $p < 0.003$]. Relapses were often delayed in the T21 group, with a mean of 8 months after IS cessation. ***Conclusion:*** Our results differ from most studies using steroids as first-line treatment where the groups were shown to have similar treatment response and T21 patients had a low risk of relapse and subsequent epilepsy. Therefore, our results suggest that vigabatrin as first-line treatment in T21 with IS may be less favorable than steroids.

RÉSUMÉ : Spasmes infantiles et trisomie 21 : des résultats peu concluants à la suite d'un traitement de première ligne à la vigabatrine. ***Introduction*** **:** Parmi les enfants qui souffrent de spasmes infantiles (SI), ceux qui sont atteints de trisomie 21 (T21) et ceux dont le développement est normal au moment de l'apparition des premiers symptômes de SI et qui ne donnent à voir aucune étiologie identifiable (désignée dans le passé comme SI « idiopathique ») sont censés voir leur état de santé évoluer de façon relativement favorable. L'objectif de cette étude est donc de déterminer, lorsque la vigabatrine est utilisée comme traitement de première ligne, dans quelle mesure il y a des différences entre ces deux groupes en termes de réponse à ce traitement, de rechute et de crises convulsives subséquentes. ***Méthodes*** **:** Dans le cadre de cette étude rétrospective, les patients ont été classés selon les groupes suivants : T21 (n = 24) et SI (n = 40 ; développement normal au moment de l'apparition des premiers symptômes de SI et aucune étiologie identifiée ; groupe témoin). Nous avons ensuite comparé entre elles leurs caractéristiques cliniques. ***Résultats*** **:** Aucune différence notable n'a émergé entre ces groupes pour ce qui est de l'âge d'apparition des premiers symptômes de SI, de la distribution selon les sexes ou d'un décalage dans l'administration du traitement. Si on les compare au groupe témoin, les individus du groupe T21 ont nécessité un nombre moyen plus élevé de traitements anticonvulsifs (3,6 contre 1,9 ; $p < 0{,}001$), ont connu davantage de rechutes [10 (42 %) contre 4 (10 %) ; $p < 0{,}005$)] et ont donné à voir un risque plus élevé de crises convulsives subséquentes [11 (46 %) contre 8 (20 %) ; $p < 0{,}003$]. À noter que les rechutes ont été souvent retardées au sein du groupe T21, la moyenne étant de 8 mois après que les SI ont cessé. ***Conclusion*** **:** Nos résultats sont ainsi différents de ceux de la plupart des études pour lesquelles des stéroïdes sont utilisés comme traitement de première ligne. Dans ces études, on a noté que les groupes en cause avaient une réponse similaire au traitement ; on a aussi observé que les individus atteints de T21 présentaient un faible risque de rechute et de crises convulsives ultérieures. De ce point de vue, nos résultats suggèrent que l'utilisation de la vigabatrine comme traitement de première ligne pour des individus atteints de T21 et aux prises avec des SI pourrait être moins favorable que celle des stéroïdes.

Keywords: West syndrome, Epileptic spasms, Infantile spasms, Trisomy 21, Down Syndrome, Vigabatrin

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Introduction

Infantile spasms (ISs) are one of the most significant seizure types in patents with trisomy 21 (T21), comprising 6–32%[1,2] of all seizures in this group. In T21, IS can result from the inherent genetic differences in brain structure or from secondary causes, such as hypoxic ischemic injury related to congenital heart disease. The genetic group more often responds to treatment with relatively low risk of subsequent epilepsy.[3]

Similarly, in the general population, 10%[4,5,6] have IS with normal development at onset and no identifiable etiology

From the Department of Pediatrics, Division of Neurology, BC Children's Hospital, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada (AND, PKHW); and Department of Diagnostic Neurophysiology, BC Children's Hospital, Vancouver, BC, Canada (AND, JC, PKHW)

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Correspondence to: Anita Datta, MD, FRCPC, CSCN Diplomate (EEG), Clinical Associate Professor of Pediatrics, University of British Columbia, BC Children's Hospital, 4480 Oak Street, Vancouver, BC V6H 3N1, Canada. Email: anita.datta@cw.bc.ca

(previously referred to as "idiopathic"[7]) and are expected to have more favorable outcome than other IS patients, including those with developmental delay at onset (previously referred to as "cryptogenic").[4,8]

In general, there has been a lack of uniformity of treatment regimens for IS, including the T21 group. However, adrenocorticotropin hormone (ACTH), high-dose prednisolone, and vigabatrin are considered as first-line therapies. Some studies have noted the possibility that children with T21 respond best to ACTH,[9,10] but controlled trials are lacking. At present, there are no significant differences reported among different treatment regimens with regard to achieving clinical remission and EEG normalization.[1,11,12]

The purpose of this retrospective study is to determine if there are differences in treatment response, relapse rates, subsequent epilepsy between patients with and without T21, with no other identified seizure etiology, and with expected developmental milestones at IS onset when vigabatrin is used as first-line treatment.

Methods

At BC Children's Hospital, all EEG results and clinical data are entered into a database, which was queried for patients with hypsarrhythmia on EEG from 1992 to 2019. The term hypsarrhythmia was used when the following criteria were met: high-voltage slowing, disorganized background, and multifocal spikes and sharp waves.[13] The term modified hypsarrhythmia was used according to the Hrachovy criteria.[14] EEGs were recorded for 25–45 minutes with Biologic or Natus machines, using the international 10–20 system with 256 Hz of sampling rate and 0.5–70 Hz of filters. The clinical records of 555 patients with hypsarrhythmia were reviewed to identify patients meeting inclusion criteria. All included patients were treated with vigabatrin as first-line therapy for IS and had at least 1 year of follow-up data. The study group ($n = 24$) was comprised of patients with a confirmed diagnosis of T21 and IS with no other severe structural abnormality to account for the etiology of IS, while the control group ($n = 40$) was comprised of patients with IS and normal development at onset and no other identified etiology. Patients with inadequate clinical information were excluded.

Clinical data, including age of IS onset, anti-seizure therapies, treatment lag, duration of IS, age of remission, IS relapse, subsequent epilepsy, family history, development, psychiatric co-morbidities, neuro-imaging, and other pertinent medical issues were obtained from the database and chart review.

Age of IS onset was based on the age the caregivers first noted IS, which was later confirmed by EEG. Treatment lag was defined as the time from age of IS onset to treatment initiation. At our institution, treatment was always initiated at the time of diagnosis. Treatment responders were defined as patients with resolution of clinical IS with EEG documenting resolution of hypsarrhythmia. Patients were considered treatment responders to vigabatrin therapy when electro-clinical cessation of IS occurred within 2 weeks after reaching the maximum target dose. This duration was chosen, as it is the standard time for EEG and clinic follow-up for such patients at our institution. If a patient responded to therapy and had relapses during a taper, they were classified as responders with recurrence. Relapse was defined as 2 weeks without reported IS followed by return of clinical IS or a return of hypsarrhythmia after resolution. This time frame was chosen, as it is a routine time period for contact with families for management decisions.

Vigabatrin dosing ranged from 75 to 200 mg/kg and was titrated to target dose based on response in a 1- to 2-week period. ACTH was initiated for 2 weeks. The majority of patients were initiated on low-dose ACTH and if IS or hypsarrhythmia continued at the end of 2 weeks, high-dose ACTH was given for an additional 2 weeks. If prednisolone was initiated, it was dosed according to the protocol in the United Kingdom Infantile Spasms Study (UKISS) for 2 weeks.[15] Steroid treatments were weaned over 4 to 8 weeks, with slower weaning schedules if the patient responded to steroids. Blood pressures, urine glucose, and fecal occult blood were routinely checked during treatment with steroids. Other later adjunctive anti-seizure medications were dosed at the discretion of the treating neurologist.

There are not many validated developmental scales specifically for children with T21.[16-18] To determine severe developmental delay, a measure previously used in T21 study[19] was implemented. If developmental milestones at the last follow-up visit were less than half of what is expected for their chronological age, they were classified as having severe developmental delay. This measure was used for both groups and determined by the quantitative descriptions by pediatric neurologists or pediatricians and by formal evaluations by developmental pediatricians. Standardized neuropsychological evaluations were not available for all patients. Autism spectrum disorder was documented if a patient had a formal diagnosis by a pediatrician.

Clinical features of the groups were compared. Statistical analysis was performed with Stata 11 software (Stata Corporation, College Station, TX). Descriptive statistics were used to characterize the cohort. Fisher's exact test and Kruskal–Wallis analysis of variance were used for categorical and continuous variables, respectively, with significance level $P < 0.05$.

Results

Clinical Characteristics

From 555 patients with hypsarrythmia in the EEG database over 28 years, 24 children with T21 and IS were identified and compared to a control group of 40 children with IS with normal development prior to seizure onset (Table 1). Both groups had no other identified etiology for seizures. The control group had variable investigations based on the discretion of the treating neurologist, including metabolic work-up, karyotype, and whole exome sequencing. All patients in the control group and 21 (88%) of the T21 group had neuro-imaging which was noncontributory to seizures.

The mean age of seizure onset was similar between the T21 and control groups: 7.6 months (range: 3–22 months) and 6.5 months (range: 2.5–19 months), respectively. There was no significant difference in sex distribution [12 males (66.6%) vs. 28 males (60.9%)] or family history of seizures [1 (4.2%) vs. 8 (20%)] between the groups.

Nine (38%) with T21 had congenital cardiac defects, such as atrial septal defect and patent ductus arteriosus, compared to one (3%) in the control group. Patients with neurological complications from other systemic conditions, such as hypoxic ischemic encephalopathy secondary to cardiac defects, were excluded. The presence of cardiac defects was not predictive of seizure control

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Table 1: Clinical findings in patients with T21 and IS versus control group

	T21 group (n = 24)	Control group (n = 40)	Significance
Mean age of onset (months)	7.6 (range 3–22)	6.5 (range 2.5–19)	Not significant
Mean treatment lag (days)	48.7 (1–365)	30.7 (1–210)	Not significant
Family history of seizures	1 (4.2%)	8 (20%)	Not significant
Number of males	12 (66.6%)	28 (60.9%	Not significant
Mean number of anti-seizure therapies	**3.6 (range 1–10)**	**1.9 (range 1–5)**	**$p < 0.001$**
Mean duration of infantile spasms (months)	**8.2 (range 1–41)**	**1.2 (range 1–9.5)**	**$p < 0.0001$**
Relapse rate	**10 (41.6%)**	**4 (28.6%)**	**$p < 0.005$**
Subsequent epilepsy	**11(45.8%)**	**8 (20%)**	**$p < 0.029$**
Lennox–Gastaut syndrome	4 (16.7%)	1 (2.5%)	Not significant
Autism	7 (29.2%)	7 (17.5%)	Not significant
Severe developmental delay	**9 (37.5%)**	**1 (2.5)**	**$p < 0.0001$**
Mean follow-up duration (years)	7.7 (range 1–19)	6.2 (range 1–19)	Not significant

Significant values are provided in bold.

or neuro-developmental outcome. Long-term follow-up was similar with a mean of 7.7 years in T21 group and 6.2 years in the control group.

Timing of Treatment and Response

The mean lag in days from IS clinical onset to treatment was not significant between the groups; 48.7 days (range: 1–365 days) in T21 group and 30.7 days (range: 1–210 days) in control group. Although all patients were treated with vigabatrin as first-line therapy, the T21 group required more adjunctive anti-seizure therapies for IS, including anti-seizure medications, ketogenic diet, and intravenous immunoglobulin [mean 3.58 (range: 1–10) vs. mean 1.9 (range: 1–5), $p < 0.001$]. Four patients were on the ketogenic diet in the study group and two in the control group for adjunctive treatment of IS.

The mean duration of IS was significantly longer in the study group: [8.2 months (range: 1–41 months) vs. 1.2 months (range: 1–9.5 months) $p < 0.0001$)], resulting in the mean age in months that the IS stopped being significantly less in the control group: [17.6 (range: 5.5–48) vs. 8.7 (range: 3–24), $p < 0.001$].

Five out of twenty-four (21%) patients with T21 and 20/40 (50%) of the control patients responded to vigabatrin monotherapy for IS. Among infants who required a second therapy for IS, 5/19 T21 patients and 2/20 control patients responded. Eleven T21 and 17 control patients required three or more medications/therapies for IS control. Three patients in the T21 group and one in the control group did not respond to any therapy and gradually evolved to Lennox–Gastaut syndrome (LGS).

Among responders, the T21 had significantly more relapses of IS: 10/21 (48%) versus 4/39 (10%), $p < 0.005$. One patient with T21 had two relapses of IS after 3 and 13 months of treatment. Relapses were often delayed in the T21 group, with a mean of 8 months after spasms cessation compared to 3 months in the control group.

Subsequent Epilepsy

The risk of later epilepsy was higher in the T21 than control groups: 11(45.8%) versus 8 (20%), $p < 0.029$. Four (16.7%) developed LGS in the T21 group and one (2.5%) in the control group.

Myoclonic seizures were more common following IS in the T21 group; 10 had subsequent myoclonic seizures and 4 reflex myoclonic seizures compared to 1 with myoclonic seizures in the control group, $p < 0.0001$. The number of therapies tried for IS and relapse was associated with later risk of epilepsy, $p < 0.001$.

Development

The study group had more patients with severe developmental delay that the control group: nine (37.5%) versus one (2.5%), $p < 0.0001$. The risk of autism [7 (29.2%) vs. 7 (17.5%)], psychiatric disorders [3 (12.5%) vs. 4 (10%)], and behavioral disorders [6 (25%) vs. 8 (20%)] was similar between the groups. In both groups, longer treatment lag time was associated with autism, $p < 0.0001$.

Discussion

T21 patients account for 3–5%,[11,20] while patients with normal development prior to onset and no identified etiology, historically referred to as "idiopathic," account for 10% of all patients with IS.[4-6] These two groups are expected to have more favorable outcome than other cohorts of patients with IS and were therefore compared.[3,4,8] However, in our study, there were a significant number of patients with subsequent epilepsy and unfavorable developmental outcome. In addition, although no difference in age of onset, treatment lag, sex distribution, or family history of epilepsy between the groups, the T21 group required more anti-seizure treatments and had longer duration of IS and more relapses than the control group when administered vigabatrin as first-line therapy.

This is in contrast to a study by Beatty et al., who also compared these two etiological groups and reported that the T21 group had lower risk of subsequent epilepsy and no relapses with ACTH as the primary treatment (mean follow-up duration in T21 group was 9.1 months).[21] Therefore, the choice of first-line treatment may have been the determining factor leading to less favorable outcome in our study. Another study examined 37 patients with IS and T21 with different treatments and concluded that the first type of treatment is the only predictor of good outcome.[10]

Some have proposed steroids are superior for IS in the T21 cohort. However, no large trials have been performed. Daniels et al. found that ACTH was the most effective treatment in a cohort of patients with variable first-line treatments.[10] Similarly, Joshi et al. demonstrated that ACTH provided the best response in a cohort of 41 T21 patients with IS. However, their results exemplify how T21 patients do not have a uniformly favorable

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Table 2: Literature review of response to therapy in patients with T21 and IS

Treatment	Literature review[1,3,9-11,19-27]
ACTH or steroid	141 (ACTH, 107; steroid, 34; not specified, 12)
Response	121 (86%)
Relapse	13 (16%)
Vigabatrin	37
Response	28 (76%)
Relapse	1 (9%)
ACTH and vigabatrin combined	17
Response	9 (53%)
Conventional anti-seizure medication	45
Response	6 (13%)

response to steroids, as response rates to first-line treatment were 71% with ACTH, 60% with oral steroids, 50% with vigabatrin, and 0% with nonstandard treatment.[22] Although hormonal therapies and vigabatrin are considered first-line therapies, treatment regimens have been heterogeneous, with variable definitions of response, relapse, and timing of treatment assessments. In review of the literature of treatment of IS in T21 (Table 2), 141 patients have been treated with steroids (ACTH, 107; steroid, 34; not specified, 12) with an 86% response rate and 16% relapse rate.[1,9-11,19-25] There are fewer reports of vigabatrin as first-line treatment, but with similar results to steroids: 37 patients have been treated with vigabatrin with a 76% response rate and 9% relapse rate.[1,10,11,22,26,27] Overall, relapse rates may be under-detected, as not all studies had long follow-up periods. Nabbout et al. did a prospective study with treatment with where 4/5 patients with T21 and IS responded to vigabatrin with IS cessation after 2 weeks and discontinuation of vigabatrin after 6 months.[26] The ICISS trial compared children with steroid treatment to a group with combined steroid and vigabatrin treatment and found no significant difference in response in patients with the addition of vigabatrin.[24] Other conventional anti-seizure medications have also been used to treat IS with poor response rates.[1,3,10,11,19,22,25]

Treatment Lag

One important predictor of developmental outcome is the starting time of appropriate therapy for IS. In our study, the time lag from onset of IS to treatment was a mean of 18.2 days longer in the T21 group, but not statistically significant. It has been previously demonstrated that treatment within 30 days of IS onset has been shown to improve outcomes, and that that a delay of a week could result in worse performance on the Vineland Adaptive Behavior Scales.[4,28-30] In the T21 population, data suggest that treatment lag of over 2 months from IS onset is associated with a longer time of cessation of IS, lower developmental quotient, more autistic features, and persistence of seizures.[20] In general, in our study, a longer treatment lag was associated with a higher risk of autism spectrum disorder. The T21 group had more severe delay and cases of LGS, despite no difference in treatment lag between the groups. The lack of effectiveness of vigabatrin as first-line treatment, represented by more anti-seizure therapies and longer IS duration, may be analogous to a longer "treatment lag" resulting in less favorable outcome in the T21 cohort.

Relapse

It is well known that despite appropriate therapy, there is a risk for relapse once IS has resolved. It is reported that children with IS of unknown etiology have a relapse rate of 10–20%.[4] In our study, a significantly higher relapse rate was noted in the T21 cohort (48%) compared to the control group (10%). Our relapse rate in the T21 is also higher than most reports in the literature, primarily using steroid as first-line treatment.[1,3,11,20,21,23,26] However, many of these studies did not have long-term follow-up of patients. Similar to our study, Sammaneechai et al. had a high relapse rate of 57% in a T21 cohort where all patients were treated with ACTH, with the median time to treatment initiation was 3.3 months and relapses occurring up to 2 years from IS cessation.[9] These results highlight the importance of long-term follow-up in T21 patients with IS, as in our study, relapses occurred up to 18 months after IS cessation and one patient had two relapses. In addition, we found that IS relapse was associated with a higher rate of subsequent epilepsy.

Subsequent Epilepsy

It is thought that compared to other cohorts of patients with IS, T21 patients have relatively better prognosis with regard to future epilepsy.[3,31] We found the risk of later epilepsy was higher in the T21 than control group: (45.8%) versus (20%). Again, this is higher than reported in most other T21 studies and may be related to our long-term follow-up durations and the fact that most studies used hormonal treatment initially.[1,3,11,20,21,23,26]

In patients with subsequent epilepsy, various other seizure types were documented with variable timing of onset, including focal, myoclonic, and generalized tonic–clonic seizures. Heterogeneous seizure types after IS are also previously reported in the literature.[1,11] Progression to LGS has been documented infrequently, relative to other groups of IS.[32] One review from 5 epilepsy centers over 30 years identified 13 T21 patients with LGS.[33] However, IS did not precede onset of LGS in any of the cases. Subsequently, there are few reported cases of LGS after West syndrome in T21.[19,23] Armstrong et al. had four patients with LGS, who all received nonstandard therapies for IS.[19] In our study, four patients with difficult to control IS developed LGS compared to one in the control group. This high number may reflect the lack of prompt IS control in our T21 cohort. It is established that myoclonic seizures and reflex seizures, commonly induced by startle, occur commonly in T21, including T21-related LGS.[34] Our study confirmed this and this is something parents may need to be counseled to look expect, as in our T21 cohort, 10 patients later developed myoclonic seizures and 4 had reflex myoclonic seizures triggered by stimuli, such as noise or emotion.

Development

In children with IS, the long-term developmental outcome is of utmost importance. Developmental assessments are challenging in the 21 population, as they have preexisting developmental

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problems either due to T21 or secondary causes. Despite no significant difference in treatment lag between the groups, the T21 group had more severe delay. This may be due to the fact that as a group, their seizures were more difficult to control, requiring more anti-seizure therapies and having more relapses and that lack of early control led to developmental sequelae. For example, the UKISS trial, which included children with various etiologies for IS, demonstrated that hormone treatment provides better initial control of IS than vigabatrin and that better initial control may lead to improved developmental outcome.[15] In our study, the risk of autism, psychiatric disorders, and behavioral disorders was similar between the groups, demonstrating how these "more favorable" cohorts still have neurodevelopmental sequelae after IS.

Some investigators have found that developmental milestones were regained after appropriate IS therapy.[11,32] However, all five children reported by Goldberg-Stern et al.[1] continued to have moderate to severe delay, autistic features, and an absence of language skills, despite seizure remission. Such was similar in our study, where children continued to have autism spectrum disorder or severe delay at long-term follow-up.

Limitations

Limitations include the fact that the majority of patients were treated with vigabatrin as first-line treatment and therefore we could not directly compare our patients to a cohort treated with hormonal therapy as first-line treatment and had to compare our results to the literature. Our results suggest that a randomized multicenter trial is needed, with standardized developmental evaluations, to compare large numbers of patients with different treatments. Additionally, children had different adjunctive therapies, timing of follow-up assessments, and EEGs, depending on the primary neurologist, a situation common in many large centers. Children with no etiology identified underwent varied evaluations, especially with regard to genetic testing, as our study spans 28 years and whole exome sequencing was not readily available in the past. Therefore, it is possible that some with an underlying genetic etiology were included in the study and affected the outcome data.

In our study, the T21 group had more refractory IS, requiring more anti-seizure therapies and longer duration of IS. Lack of good initial control in these patients may have led to the higher risk of subsequent epilepsy and severe developmental delay at long-term follow-up. Our results differ from previous studies using steroids as first-line treatment, where the two groups had similar treatment response and T21 patients had a low risk or relapses and subsequent epilepsy.[21] Vigabatrin as first-line treatment may have been the reason for these differences. The study results also highlight that close long-term observation of patients with IS and T21 is important as they had a higher risk of relapse, which can be delayed by over 1 year. Overall, our results are suggestive that vigabatrin as first-line treatment in IS and T21 is less favorable than steroids.

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Conflicts of Interests

The Authors declare that there is no conflict of interest.

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Statement of Authorship

AD developed the original concept and study design of the manuscript. She obtained clinical data by performing a detailed chart review and entering the data in a spreadsheet. She did a literature review on the subject and created the tables. She helped to analyze the data, drafted the manuscript, and then reviewed and edited it for important intellectual content.

JC participated in identifying eligible patients. She also helped to analyze the data. She reviewed and edited the manuscript for important intellectual content.

PKHW created the EEG database, which was crucial to identify patients. He provided guidance in study design and analysis. He reviewed and edited the manuscript for important intellectual content.

All authors gave approval to the final version of the manuscript to be submitted and all authors are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval

H19-02543-A002

Disclosures

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