A Review of Dental Outcomes for Infants and Preschool Children Enrolled into a Clinical Trial of Asfotase Alfa for Early Onset Hypophosphatasia

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Abstract

Introduction: Hypophosphatasia (HPP) is a highly variable genetic disease that impedes the development of teeth and bones. HPP is due to mutations in the *ALPL* gene which encodes the tissue non-specific form of alkaline phosphatase (TNSALP). Dental manifestations of HPP include painless premature exfoliation of primary teeth with intact roots. Until recently, there was no effective treatment for this disorder. Asfotase alfa is human recombinant bone-targeted ALP (Strensiq^{TM}) (Alexion Pharmaceuticals, Inc. Boston, MA, USA). The purpose of this study was to review the development and exfoliation patterns of primary and permanent teeth in HPP patients with systemic HPP who were enrolled at the Canadian site in Winnipeg in a clinical trial of enzyme replacement therapy (ERT) with asfotase alfa.

Methods: Data were collected from a cohort of hypophosphatasia patients ≤ 5 years of age at baseline who were enrolled at the Winnipeg site from locations across North America. Available dental data were recorded from a review of study files of enrolled patients at scheduled visits. In particular, exfoliation patterns and the eruption of deciduous and permanent teeth. Statistical analysis included descriptive and bivariate statistics (T tests and chi square analysis). A p value ≤ 0.05 was significant.

Results: Eleven children (7 females, 4 males) with a mean age of 30 ± 27.1 months were enrolled at the Manitoba site in this 72-month clinical trial. Five were recruited in infancy (mean age 3.0 ± 2.3 months) while the other 6 were recruited as preschool children (mean age 52.5 ± 11.3months). Overall, children recruited as preschoolers had lost an average of 10.2 ± 3.9 of primary teeth prematurely due to HPP before enrollment. On average, children lost 2.3 ± 2.9 number of teeth during this clinical trial. Participants recruited as infants prematurely lost

significantly fewer teeth to early onset HPP during the trial period where started on ERT in infancy than those who were recruited as preschoolers and started on ERT at a later age (1.9 $\pm$ 2.1 teeth vs. 10.2 $\pm$ 3.9, p= 0.0043).

Conclusion: Results suggest that there were fewer teeth prematurely lost because of HPP among children who began asfotase alfa treatment in infancy compared to those children recruited as preschoolers. This is the first demonstration, albeit on a small number of patients, that the oral health of children with confirmed systemic HPP with onset of signs and symptoms < 6 months of age might be improved with earlier and continued administration of ERT vs. later initiation of ERT.

Introduction

Hypophosphatasia (HPP) is a rare highly variable hereditary disease that has a broad range of severity affecting individuals of various stages in life. Statistics show that one in every 100,000 individuals in the general Canadian population and one in every 300,000 Europeans are affected[2 3]. HPP results from mutations in the *ALPL* gene on chromosome 1p36.12, leading to deficiency of tissue nonspecific alkaline phosphatase (TNSALP). TNSALP is abundantly expressed in liver, bones, kidneys and other cell types. In HPP, a lack of TNSALP causes an excessive build-up of its endogenous substrates which leads to a plethora of systemic complications. Inorganic pyrophosphate (PPi) is one of the accumulated endogenous substrates and has been shown to have inhibitory effects on the mineralization of bones and teeth[2]. Systemic manifestations of HPP range from marked skeletal undermineralization with rickets, fractures and skeletal deformities, to respiratory failure due to undermineralized rib cage and lung hypoplasia and to premature loss of primary dentition with intact roots.

The processes involved in normal mineralization are complex. The end result is precipitation of calcium and phosphate as hydroxyapatite (HA) crystals in collagen fibrils in the extracellular matrix and within matrix vesicles released from osteoblasts and chondroblasts. The vesicles release their contents into the collagenous matrix. In teeth particularly, HA plays a major role in the formation of dentin and cementum. Cementum is essential for providing the attachment site for periodontal ligaments to the alveolar bone. However, in HPP, the mineralization of HA is inhibited, ultimately results in dental consequences. The atraumatic loss of primary teeth is one of hallmarks of HPP and a distinguishing symptom of HPP because of the absence of cementum on roots[6]. Dental manifestations other than premature loss of primary

teeth include decrease in height of alveolar bone, malocclusions, enlarged pulp chambers, as well as enamel hypoplasia[19].

There are more than 340 known *ALPL* mutations associated with HPP [8]. There is poor genotype-phenotype correlation in this highly variable disorder. There are many different categories of HPP historically classified based on age of onset of signs and symptoms(see Table 1). More very severe forms of HPP are felt to be due to autosomal recessive mutations while milder forms of HPP are felt to be autosomal dominant[9]. There appears to be a correlation of severity of symptoms to the age at which HPP is diagnosed; the earlier the onset of the disease, the more severe the disease.

There are six categories of HPP, each based on the age of onset of the disease. They include: prenatal/perinatal benign, perinatal lethal, infantile, childhood, adult, and odonto-HPP. Patients within all these categories experience varying symptoms related to bone, dental, respiratory, motor and vitamin deficiency. The most severe form of HPP is perinatal lethal. Historically, stillbirth and death within weeks before or after birth occurred in the perinatal form and the mortality rate in the infantile form (with onset of symptoms before 6 months of age) has been seen 50-100% in some populations (8,20,23). The least severe form of HPP is odonto-HPP as these patients only experience dental symptoms. The lack of mineralization of dentin, absence of cementum, and alveolar bone does not provide adequate anchorage for teeth, thus causing premature exfoliation of primary teeth without history of trauma or inflammation[13]. Further details regarding the summary of the categories of HPP and current treatment can be found in Table 1.

Asfotase alfa (Strensiq™) has been developed as an effective enzyme replacement therapy (ERT) to treat pediatric- onset (perinatal, infantile and childhood) HPP. ERT with asfotase alfa is the only treatment available and has been approved in countries including USA, Canada, Japan and Europe[19]. It is a human-recombinant enzyme with a deca-aspartate tail that targets the molecule to bone and teeth[14,15]. Subcutaneous injections with asfotase alfa targeted to bone cause the release of inorganic phosphate (Pi) from the substrate PPi and thus in combination with calcium will allow the propagation and mineral formation of calcium phosphate hydroxyapatite crystals[6].

Recent studies involving asfotase alfa in infants and children with HPP have shown improvements in systemic outcomes. (20,23,25). Radiographic and clinical parameters show improved skeletal mineralization, healing of rickets, decreased need for respiratory ventilator support, as well as overall improvement in growth and strength in physical function with an excellent safety profile[15]. Prior to human trials with ERT, there have been experiments with animal models of HPP in "knockout" mice showing improvements in survival, skeletal mineralization and stabilization in molar dentition[6]. Further, mice models have shown that asfotase alfa prevents skeletal abnormalities as well as improves mineralization of the enamel organ, thus halts tooth loss and restores the acellular cementum[15].

A recent study funded by Alexion involving 16 patients explored the dental outcomes using ERT on infantile and childhood forms of HPP. This clinical study took into account the participants' alkaline phosphatase (ALP) levels, periodontal and radiographic records. Results showed a positive stabilization with complete lack of mobility of the remaining teeth[19]. It was also revealed that participants who reported premature exfoliation of primary anterior and

posterior teeth had lower levels of ALP than those who solely had premature loss of primary anterior teeth[19].

The aim of this study was to review the development and exfoliation patterns of primary and permanent teeth in infants and children with HPP to examine the efficacy of the ERT treatment using asfotase alfa, a human recombinant bone-targeted ALP (Strensiq™)

Methods

This study reviewed dental data of 11 infants and children diagnosed with confirmed HPP at ≤ 6 months of age and followed for 72 months at the Canadian site of the open-label, multicenter, single-arm, multinational study of the efficacy and pharmacokinetics of asfotase alfa (ClinicalTrials.gov NCT01176266; EUDRACT 2010-019850-42). The total number of children enrolled in this study globally was 69 at 22 sites in 12 countries. This study was approved by Biomedical Research Ethics Board (BREB) at the University of Manitoba (#B2010:073). Asfotase alfa was provided by Alexion Pharmaceuticals Inc., the study sponsor. Clinical data on eruption and premature exfoliation of deciduous teeth among children with HPP receiving asfotase alfa were assessed. Dental data were captured from the study visit screening form, which included information on the number of primary teeth prematurely exfoliated and the number of primary and permanent teeth erupted. During the clinical trial visits, oral examinations were performed by one experienced dentist to record the number of teeth in the oral cavity and to determine number of deciduous teeth erupted and lost. The identity of the deciduous teeth erupted and lost were also recorded. The efficacy of asfotase alfa was evaluated based on the number of deciduous teeth erupted and lost.

Study participants recruited were 11 infants and children diagnosed at ≤ 6 months of age and who were ≤5 years at the time of enrollment. Clinical visits for clinical trial were performed at the Children's Hospital of Research Institute Manitoba (CHRIM) in Winnipeg, Canada. Site visits were at weeks 3 and 6 after enrollment, and at months 3, 6, 9, 12, 15, 18, 24 and then every 6 months until study termination. Participating infants $\leq$ 6 months were required to stay in Winnipeg for the first 24 weeks of the study. The total duration of the study was over a period of time of 72 months. For the data analysis the Winnipeg subjects were divided into the study participants recruited in infancy (n=5) and study participants recruited at preschool age (n=6) (see Results).

Patients were administered dosages of asfotase alfa subcutaneously at 6 mg/kg per week. The options included 1 mg/kg 6 times per week or 2 mg/kg 3 times per week, depending on parental preference. The maximum dose of drug administered was 40 mg per injection or 9 mg/kg/wk in Australia, France, Germany, Italy, Saudi Arabia, Spain, and the United Kingdom; no dose restrictions were applied in Canada, Japan, Russia, Turkey, or the United States (Hofman ref 25). Asfotase alfa is a clear, colorless aqueous solution consisted of 25 mM sodium phosphate, 150 mM sodium chloride, pH of 7.2-7.6. Adjustments to the dosage were made throughout the clinical study with formal protocol amendments submitted to REB to accommodate the changes in body weight as well as the patient's response to ERT treatment.

At baseline and at each follow up visit fasting blood and urine samples were taken to examine the blood serum ALP level, plasma pyridoxal phosphate (PLP) (another endogenous substrate for TNSALP), PPi, serum calcium and phosphate levels, and other general hematologic parameters. Data analysis included descriptive statistics (e.g. frequencies, means ± standard

deviation (SD)) and bivariate analyses (t tests and chi square analysis). A p value of ≤ 0.05 was statistically significant.

Results

Eleven children were enrolled into the clinical study at the Winnipeg site and followed between the years 2010 and 2016. The mean age at enrollment was 30 ± 27.1 months and 64% were female. The majority of these 11 children were from Canada and the United States. The ages of participants at enrollment can be seen at Table 2, revealing that many were at different stages of development in the primary dentition. Five children were recruited in infancy, most often at birth (mean age 3.0 ± 2.3 months) while the remaining six were recruited as preschoolers (mean age 52.5 ± 11.3 months). One of the 5 participants in the infant group died before the 9-month study visit due to complications of early onset HPP.

At enrollment in the clinical trial, participants' baseline dental assessments recorded the number of primary teeth already exfoliated. The mean number of prematurely exfoliated primary teeth due to HPP among all participating children before enrollment was 5.5 ± 6.0 (median = 4.0). Within the infant group, understandably, there were no prematurely lost primary teeth due to HPP because no child was dentate. In contrast, the 6 participants in the preschool group had prematurely lost a mean of 10.2 ± 3.9 (median 11.5) primary teeth prior to enrollment. The type of prematurely exfoliated primary teeth among the six children in the preschool group is reported in Table 2. All 6 participants had lost an incisor, half prematurely exfoliated a canine, while one third had lost a molar prematurely.

Among the entire Winnipeg cohort, the mean number of primary teeth prematurely exfoliated due to HPP during the clinical trial was 2.3 ± 2.9 (median 1.5). Figure 2 revealed that

2 children in the infant group had lost primary teeth while 4 children in the preschool group lost primary teeth during the trial (Figure 3). In the infant group, the mean number of primary teeth prematurely exfoliated because of HPP during the trial was 1.9 ± 2.1 (median = 1.5) (Table 2, Figure 2). When examining the type of primary teeth exfoliated because of HPP for those in the infant group during the trial, 2 had lost incisors and 1 had lost a molar.

In the preschool group, the mean for the number of primary teeth exfoliated during trial was 2.7 ± 3.4 (median 1.5) (Table 2, Figure 3). The type of primary teeth exfoliated included incisors, canines and molars.

T test analysis was then performed to compare the mean number of prematurely exfoliated primary teeth in children to the infant group who received the intervention soon after birth with the number of prematurely exfoliated primary teeth due to HPP among children in the older age group before their participation in the clinical trial. This permitted a comparison between an infant group receiving early treatment compared to older children who did not begin ERT soon after of birth. Results from this T test analysis revealed that children in the infant group had a statistically significant lower mean number of prematurely exfoliated teeth during the study period compared to the mean number of teeth exfoliated in the older age group before commencing the study (1.9 ± 2.1 teeth vs. 10.2 ± 3.9), p= 0.0043.

During the course of the clinical trial, each participant's number of erupted primary and permanent teeth and exfoliated primary teeth were recorded (Table 2, Figure 2, Figure 3). The mean for the number of teeth erupted during trial for all participants was 8.4 ± 6.6 (median 8). This value included both erupted primary and permanent teeth. Children in the infant group had an average of 10.4 ± 7.3 (median = 12) recorded primary teeth erupted during the trial

observation period. This result was higher when compared to the preschool group's mean of 6.7 ± 6.2 (median = 7). The number of teeth erupted during the clinical trial are illustrated in Figure 2 and 3, which demonstrates the changes for each participant in the infant and preschool group over the timeline of the trial.

Discussion

HPP is a metabolic disorder leading malformation of bones and teeth. The disease entails a wide spectrum of symptoms and a defining dental clinical symptom is premature exfoliation of primary teeth with intact roots.

Our study examined the exfoliation patterns of primary and permanent teeth for 11 infants and preschool children with HPP participating at the Winnipeg site as part of a global ERT open label trial (n=69). During the clinical trial, the average number of teeth exfoliated in the infant group was fewer than what the preschool group experienced prior to participating in this ERT trial. The transition to mixed dentition stage for the preschool group should be considered when evaluating the exfoliation and eruption values. Key finding revealed that infants followed at our site who received ERT shortly after birth showed significant decrease in premature exfoliation of primary teeth as compared to children who did not enroll for treatment until preschool years. This suggested that the age at which ERT commences may be critical in predicting the dental outcome of children with early onset infantile HPP.

Our results correlate with published studies where premature exfoliation of primary incisors preceded the exfoliation of posterior teeth and that exfoliation of posterior teeth indicates increased severity of HPP[21]. This was observed when all of the 6 preschool children with HPP at enrollment had lost their incisors as these are often the first teeth to be affected[2]. This effect was minimized in the infant group who received asfotase alfa shortly after birth as

results showed that only 2 out of the 5 participants had prematurely exfoliated primary incisors during the study trial. A study conducted on mice with HPP that showed improved dental outcomes in molar development and mineralization when administered intestinal like chimeric alkaline phosphatase[6]. This animal study predicted improvements in dental development in HPP participants now confirmed and highlighted in the findings of our clinical trial.

A recently published study on another study involving children with HPP treated with asfotase alfa reported similar findings to ours in this clinical trial. Results in the study showed notable improvements in terms of lack of mobility of remaining primary teeth, this was particularly apparent in one of the youngest patients enrolled in the trial at 2.5 years of age[19]. Conclusions from that study were similar to our finding that timely administration of ERT is critical for minimizing negative dental outcomes in systemic HPP patients.

This study is not without limitations. Due to early onset HPP being a rare genetic disease, our study only involved the 11 children at our site but data from the entire study cohort of 69 children globally are not available. However, the number of patients followed at our site is remarkable given how rare this condition is. Despite the small sample size of this clinical trial at our site with asfotase alfa, we were able to observe a statistically significant reduction in prematurely exfoliated primary teeth in those who receive ERT soon after birth. One infant participant died prior to 9 months into treatment due to complications of HPP. Despite there being meticulous adherence to study protocols and data collection during study visits, dental data were not available for every child at all points in time as some children missed dental assessment visits. Furthermore, dental radiographs were not available to assess mineralization and root development of teeth and determine caries status. Therefore, it may be

possible that some teeth we determined to be prematurely lost to HPP might have also been a result of caries. However, we normally queried parents on the reason for loss of any primary teeth.

This study addresses the importance of early diagnosis and intervention for early onset HPP. Although HPP can be misdiagnosed as rickets, osteomalacia, osteogenesis imperfecta, the blood test for low ALP can be done to verify diagnosis and furthermore, elevated serum PLP can support the diagnosis of HPP. Presently, asfotase alfa is the only treatment that has been approved and demonstrated improvements in infants and children with HPP[19]. In terms of managing the premature exfoliation of primary teeth, partial dentures have been valuable in restoring function and in preventing space problems in the arch[19].

Dentists play a crucial role in early recognition of the disease as premature exfoliation of primary teeth is a hallmark odonto-HPP. First dental visits are recommended to be before or at twelve months and therefore, this makes dentists one of the first healthcare providers for recognition and referral for treatment of HPP. This prevents delay in diagnosis as well as managing preventable HPP symptoms.

Parents of children with HPP can still take steps to care for their children's teeth and prevent caries. Parents are advised to provide a grain sized fluoride toothpaste if their child is under three years of age. Children over three years of age will benefit from a pea sized amount of fluoride toothpaste and should have parental assistance with brushing until eight years old. Prevention of caries can also be achieved by attending regular dental visits and limiting snacks and sugary drinks in between meals. Dental sealants may also be a preventative restorative

measure. Placing restorations over enamel defects may also help minimize the risk of caries onset and progression.

Ongoing dental follow-up is recommended for children on ERT for early onset HPP. Future investigations on the dental outcomes associated with asfotase alfa might include full clinical charting of caries and periodontal status, including radiographs, along with exfoliation and eruption data. Records from participants' routine dental visits would also be valuable in such clinical studies. A more detailed follow up and longitudinal studies would also be of interest.

Conclusion

Analysis of the Winnipeg cohort of 11 patients enrolled in the NCT01176266 trial (ClinicalTrials.gov NCT01176266; EUDRACT 2010-019850-42) found that infants receiving asfotase alfa had significantly fewer prematurely exfoliated primary teeth compared to the baseline exfoliation status of preschool children before they commenced ERT. This illustrates that age at which ERT commences may play a critical factor in alleviating the dental symptoms of early onset HPP. Further analysis of the larger cohort of children enrolled in this clinical trial (n=69) will be important.

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Table 1. Categories of Hypophosphatasia

Types of HPP	Age of onset	Symptoms	Treatment
Perinatal lethal[3]	End or gestation or at birth	- Sometimes complete absence of bone - Detected by ultrasound	Asfotase Alfa
Prenatal/perinatal benign[2 5 3]	End of gestation or at birth	- In utero skeletal deformities could improve over time - Short limbs - Chest deformity - Respiratory distress - Wide fontanels - Detected by ultrasound	- -
Infantile HPP[2 5]	Before 6 months of age	- Most severely affected - Epilepsy - Respiratory complications - Pyridoxine dependent seizures, may also be associated with fever, irritability, myelophthisic anemia and intracranial hemorrhage	- Asfotase Alfa
Childhood HPP[10 3]	After 6 months of age	- Large dental pulp - Premature exfoliation of teeth - Lack of cementum - Irregular dentin formation - Low bone height - Bony defects in mobile primary teeth - Abnormal alveolar bone resorption - Delayed walking	- Asfotase Alfa
Adult HPP[8 11]		- Atraumatic premature loss of deciduous teeth - Muscle pain, weakness, elevating cranial pressure, recurring stress fractures, osteomalacia, chondromalacias, renal compromise - History of rickets - Early exfoliation of permanent teeth - Nephroncalcinosis from hypercalcemia and hypercalciuria causing renal compromise - PPi arthropathy resulting in pseudogout	
Odonto-HPP[10]	Any age	- No radiographic evidence - Atraumatic premature loss of deciduous teeth - Root intact during tooth loss - Enamel thinning	

Table 2. Characteristics of children and infants enrolled into ENB 010-10 study including premature exfoliation of primary teeth

Participant	Age at Baseline (months)	No. Primary Teeth Exfoliated before Enrollment	Type of Primary Teeth Exfoliated before Enrollment	No. Primary Teeth Present at Enrollment	No. Primary Teeth Exfoliated during Trial	Type of Primary Teeth Exfoliated during Trial	No. Teeth Erupted during Trial
Infant Group (Sex)							
1 (F)	4	0	N/A	0	4	Incisors, molars	12
2 (M)	1	0	N/A	0	3	Incisors	20
7(M) *	0	0	N/A	0			0
8 (F)	5	0	N/A	0	0		12
9 (F)	5	0	N/A	0	0		8
Total Infant Group (N=5)	Mean= 3.0 ± 2.3	Mean=0 Median=0	N/A	Mean= 0 Median=0	Mean= 1.9 ± 2.1 Median=1.5	Incisors and molars	Mean= 10.4 ± 7.3 Median=12
Preschool Group							
3 (F)	66	12	Incisors, canines	8	2	Molars	6
4 (F)	60	7	Incisors	13	9	Incisors, canines, molars	10
5 (M)	54	13	Incisors, canines, molars	7	4	Canines, molars	16
6 (F)	42	14	Incisors, canines, molars	6	0	N/A	8
10 (F)	36	11	Incisors, canines	9	1	Canine	0
11 (M)	57	4	Incisors	16	0	N/A	0
Total Preschool Group (N=6)	Mean= 52.5 ± 11.3	Mean= 10.2 ± 3.9 Median=11.5	Incisors, canines and molars	Mean=9.8± 3.9 Median=8.5	Mean=2.7 ± 3.4 Median=1.5	Incisors, canines and molars	Mean=6.7 ± 6.2 Median=7
Total (N = 11)	30 ± 27.1	Mean=5.5 ± 6.0 Median=4.0	Incisors, canines and molars	Mean=5.4 ± 5.8 Median=6	Mean=2.3 ± 2.9 Median=1.5	Incisors, canines, and molars	Mean=8.4 ± 6.6 Median=8

*deceased before 9 months

Figure 1. Clinical assessments and documentation at various stages of Asfotase Alfa study trial. Note the dental assessments that were recorded per visit to evaluate the effect of the enzyme replacement therapy on mineralization of teeth and alveolar bone.

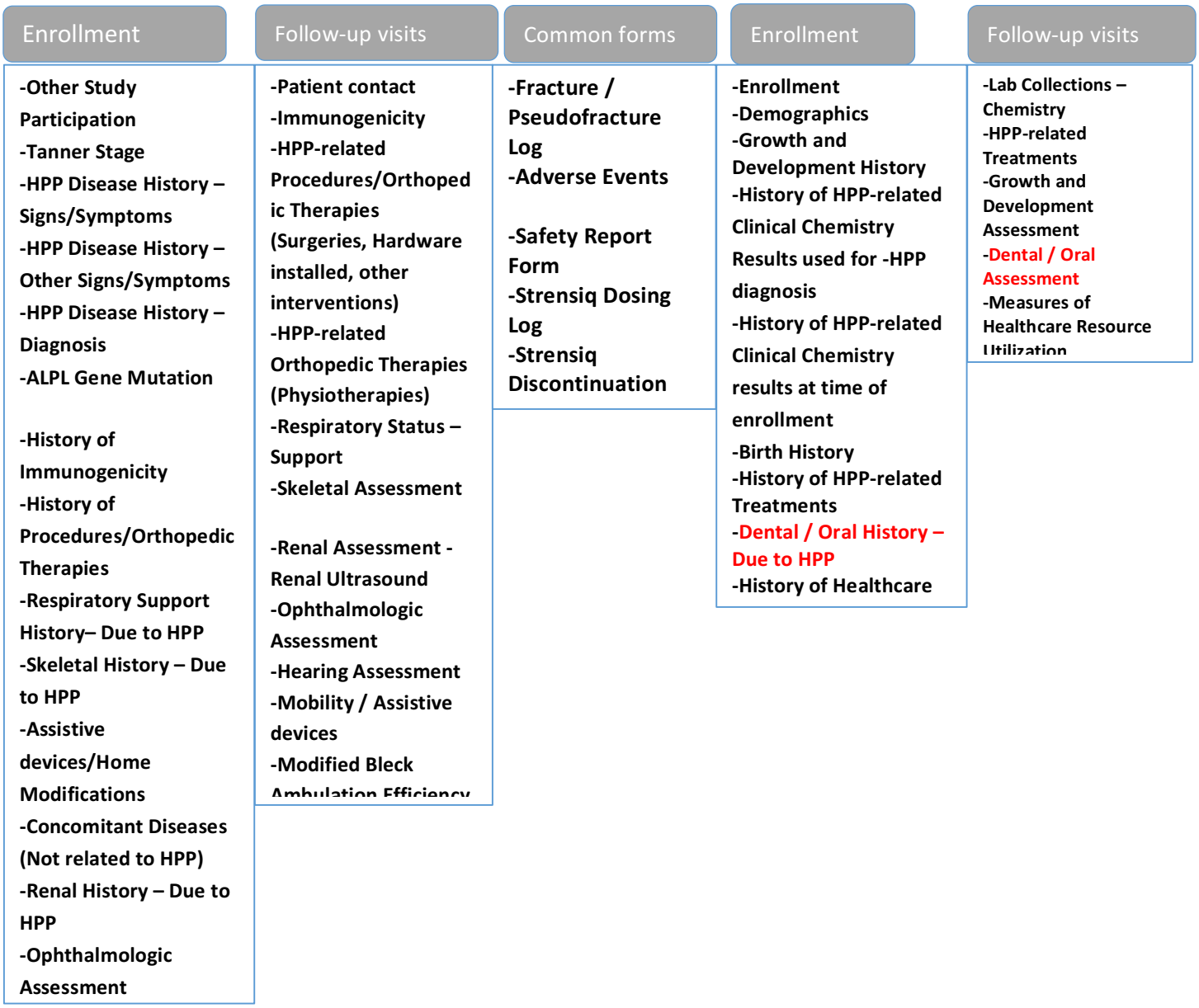
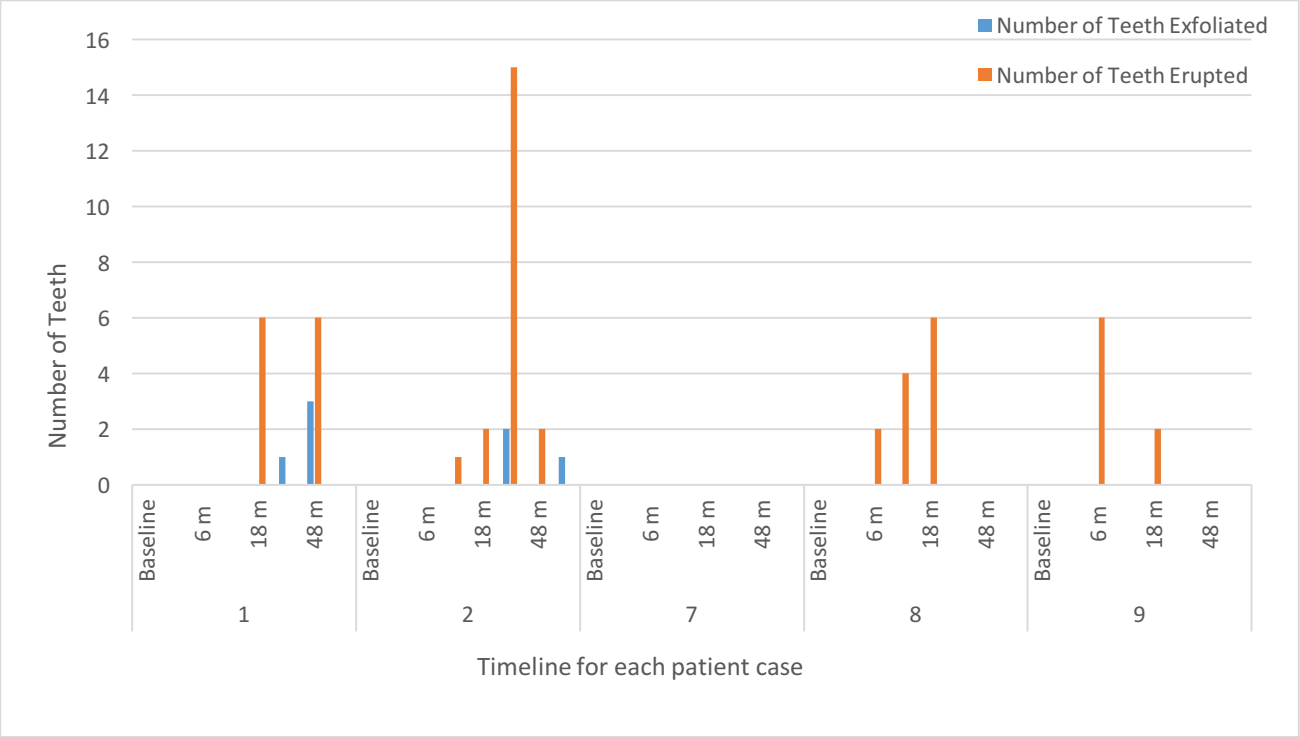


Figure 2. Distribution of teeth prematurely exfoliated and erupted for children in the infant group during the trial period



*participant 7 deceased before 9 months

Figure 3. Distribution of teeth prematurely exfoliated and erupted for children in the preschool group during the trial period