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Home infusion with Elosulfase alpha (Vimizim^{R}) in a UK Paediatric setting

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ABSTRACT

Enzyme replacement therapy is the only available treatment for Mucopolysaccharidosis type IVA (MPS IVA, Morquio syndrome). The treatment is lengthy and invasive involving weekly intravenous infusions of 4–5 h. This can cause significant disruption to normal family life so the provision of a safe and effective homecare service is essential. In order to deliver a safe service, robust standards must be in place; this includes appropriately trained members of homecare staff, detailed management for infusion related reactions (IRR) and appropriate venous access. In this report we demonstrate the criteria required to ensure a successful home treatment programme and describe our experience thus far.

1. Introduction

Mucopolysaccharidosis type IVA (MPS IVA, Morquio A Syndrome) is an autosomal recessive lysosomal storage disease (LSD) caused by a deficiency in the enzyme *N*-acetylgalactosamine-6-sulfatase (GALNS) due to a mutation in the GALNS gene located on chromosome 16q24.3 [1]. Infants with MPSIVA usually appear normal at birth, however, due to the accumulation of storage material in tissues and organs, leading to cellular dysfunction they progressively develop profound skeletal and joint abnormalities alongside a range of non-skeletal manifestations [2,3,4]. Such manifestations can include impaired respiratory function, valvular heart disease, obstructive sleep apnoea, hearing impairment, corneal clouding, spinal cord compression and dental abnormalities [5].

Morquio A syndrome can often be distinguished from other types of MPS disorders by a typical short trunk dwarfism with a short neck; skeletal manifestations tend to be more extensive than in other MPS disorders. Alongside this, hypermobility of distal joints is a significant feature and is characteristic of Morquio A syndrome [6]; Morquio A syndrome has not been associated with cognitive impairment [7].

The most common gene mutation is present in < 9% of Morquio patients giving rise to a wide heterogeneity with regard to clinical presentation, severity of disease and rate of progression [8]. Some patients may present with a more classical phenotype associated with short stature and severe skeletal and joint abnormalities, whereas some patients do not have a characteristic presentation but may show atypical signs such as hip stiffness and pain. Attenuated patients tend to present later in life, are taller and have less spinal disease. Due to the heterogeneous and progressive nature of the disease, the management of patients is often challenging and requires a multidisciplinary approach [6].

In April 2014, Elosulfase alpha (Vimizim) was licensed in the EU and funded as a treatment for MPS IVA in the UK by NICE (National Institute for Health and Care Excellence) in December 2015. It is delivered on a weekly basis via an intravenous infusion over an average of four to five hours. Findings from the clinical trials involving a total of 235 patients with Morquio syndrome showed that Vimizim significantly improved endurance, decreased urinary KS levels and was generally well tolerated [9]. Of the 235 patients enrolled in the clinical trial, 16 (6.8%) experienced signs and symptoms consistent with anaphylaxis. The timing of these reactions were often as early as 30 min after the beginning of the infusion to 3 h after the completion of the infusion. All but two were able to receive further infusions of Elosulfase alpha with infusion rate adjustment and/or medical intervention [10,11]. Based on the outcome of the phase 1 and 2 study, a multicenter, double blind, placebo controlled phase 3 study was performed to assess the efficacy and safety of infusions with Elosulfase alfa 2.0 mg/kg every week and every other week [12]. The study showed significant improvement in endurance of 22.5 m in 6MWT distance during 24 weeks of treatment with Elosulfase alfa at 2.0/mg/kg/week as compared with placebo. No significant impact was observed with alternate weekly dosing [6].Vimizim is shown to provide positive and meaningful changes in several clinical parameters. Treatment should be commenced as soon as possible after diagnosis is made; however results of treatment may be variable due to the significant heterogeneity of the condition [5].

Although ERT has been proven to be effective, there are many factors that impact upon both the patient and their families. It is invasive, and the prolonged infusion time often requires time off school,

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work or college. The families often have to travel a significant distance to a dedicated treatment centre such as our own which can often cause a financial burden. Many patients may find frequents visit stressful and time consuming whilst hospital visits may reduce feelings of frustration and isolation as they are often given the opportunity to meet other families and patients suffering with the same condition [13,14]. By transferring into homecare perceived benefits may include less disruption to activities of daily living, less disruption to normal family life and more involvement in their own care leading to greater independence [14]. Home therapy allows to alleviate the long term burden of a lifelong therapy and has been shown to significantly improve compliance by effectively avoiding missed infusions due to non-clinical reasons and increasing scheduling flexibility [20,21]. Long term compliance is vital in order to maintain the efficacy of enzyme replacement therapy as suggested in long term studies for other forms of MPS disorders [17,18,19] therefore the importance of delivering treatment is a convenient setting for the patient and family is vital.

There are also risks associated with home therapy including the possibility of infusion related reactions (IRR) when the patient is not in a hospital environment, this may vary from minor pyrexia or a rash to a full anaphylactoid reaction. Therefore, it is vital that patients are selected for homecare in order to maximize the benefits and minimize the risks. Nevertheless, despite these Fig. 1 risks patients with LSD's still prefer home therapy [13,14 and 15]. In this publication we review our experience with home enzyme replacement therapy treatment in children with MPS IVA and demonstrate the criteria required to ensure a successful home treatment programme.

2. Patients and methods

Patient demographics, clinical features, infusion related reactions (IRR) and the use of pre-medications are indicated in Tables 1 and 2. The details of Vimizim dosing are given in Table 3.

3. Criteria followed for the safe transfer of patients to home therapy

The below criteria demonstrate the criteria used to select the patient cohort described in Tables 1 and 2 for a safe transfer to home therapy.

4. Patient

4.1. Fully established on Elosulfase alpha

Patients need to be stable on Elosulfase alpha with either no IRR's or IRR's that have been managed appropriately. Some patients may never experience an IRR. However, if this does occur reactions need to be managed in an appropriate manner with adjustment in their pre-medication regime and/or infusion rate changes in order to stabilize the patient in a hospital setting prior to transfer. The minimum duration of before transition to the home setting should be 12 weeks.

Fig. 1. Patient receiving Vimizim in the hospital and homecare setting.

Table 1
Patient demographics.

Number of MPS IVA	23
Number treated with Vimizim in centre	20 (14 currently on homecare) 3 untreated 6 treated at other centre's
Age range	4–16 years
Average age at diagnosis	46.6 months (3.88 years)
Severe: Attenuated	18:5 (12:2 currently on homecare)
Number on nocturnal respiratory support	30%

Table 2
Homecare data from the 14 patients.

Total number of LSD patients (all children) receiving any homecare ERT at the center	71
IRRs in hospital	6 (42.8% of current patients)
Use of pre-medications	14 (100%)[a]
Duration of ERT in hospital prior to home treatment (weeks)	10–15 weeks[b]
Duration of ERT at home in weeks (at time of reporting)	18–200 (mean–109)
Number now having school based infusions	6
Number of current patients using TIVAD's for treatment	10 (71.4%)
Number of patients using weekly cannulation for treatment	4 (28.6%)

[a] As mandated from clinical trial protocols.
[b] These figures are based on treatment naive patients only as those on clinical trials remained in hospital for a longer period before transition to home infusions.

Table 3
Infusion details for Elosulfase alpha (Vimizim) [6].

Vimizim		
Dose	2 mg/kg weekly	
Dilution	< 25 kg: dilute in 100 ml of 0.9% saline > 25 kg: dilute in 250 ml 0.9% saline	
Rate of administration	In 100 ml:	In 250 ml:
	Start rate 3 ml/h	Start rate 6 ml/h
	After 15 min, 6 ml/h	After 15 min, 12 ml/h
	After 15 min, 12 ml/h	After 15 min, 24 ml/h
	After 15 min, 18 ml/h	After 15 min, 36 ml/h
	After 15 min, 24 ml/h	After 15 min, 48 ml/h
	After 15 min, 30 ml,hr.	After 15 min, 60 ml,hr.
	After 15 min, 36mlhr	After 15 min, 72mlhr
Total duration of infusion	4–5 h	

4.2. Established intravenous access

The patient should have good peripheral venous access or a totally implanted venous access device (TIVAD) in situ. The family should also be aware of how to care for such devices and the risks that are associated with these. Such risks may include line infections, swelling, redness and to avoid close contact sports that may knock or damage the TIVAD. Within the hospital setting there is also a robust service provided by the play therapy team, who are vital when assisting younger children who are needle phobic.