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Vosoritide Therapy in Children with Achondroplasia: Early Experience and Practical Considerations for Clinical Practice

Semler O[1], Cormier-Daire V[2], Lausch E[3], Bober MB[4], Carroll R[4], Sousa SB[5], Deyle D[6], Faden M[7], Hartmann G[8], Huser A[9], Legare J[10], Mohnike K[11], Rohrer T[12], Rutsch F[13], Smith P[14], Travessa A[15], Verado A[16], White K[17], Wilcox W[18], Hoover-Fong J[19]

[1]Faculty of Medicine and University Hospital Cologne, Center for Rare Diseases, University of Cologne, Cologne, Germany; [2]Centre of Reference for Constitutional Bone Diseases (MOC), Department of Clinical Genetics, Paris Centre University, INSERM UMR 1163, Imagine Institute, Necker-Enfants Malades Hospital, Paris, France; [3]Pediatric Genetics, Center for Pediatric and Adolescent Medicine, University Hospital Freiburg, Freiburg, Germany; [4]Nemours Skeletal Dysplasia Program, Nemours Children's Hospital – Delaware, Wilmington, Delaware, United States; [5]Medical Genetics Unit, Hospital Pediátrico, Centro Hospitalar e Universitário de Coimbra; and University Clinic of Genetics, Faculty of Medicine, Universidade de Coimbra, Coimbra, Portugal; [6]Department of Clinical Genomics, Mayo Clinic, Rochester, Minnesota, United States; [7]Medical Genetic Unit, Children's Hospital, King Saud Medical City, Riyadh, Saudi Arabia; [8]Vienna Bone and Growth Center, Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Austria; [9]Paley Advanced Limb Lengthening Institute, West Palm Beach, Florida, United States; [10]Department of Pediatrics, University of Wisconsin, Madison, Wisconsin, USA; [11]Universitätskinderklinik, Otto-von-Guericke Universität, Magdeburg, Germany; [12]Clinic for General Pediatrics and Neonatology, Universität des Saarlandes, Saarbrücken, Germany; [13]Münster University Children's Hospital, Münster, Germany; [14]Division of Endocrinology, Phoenix Children's, Phoenix, Arizona, United States; [15]Department of Medical Genetics, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, and Faculty of Medicine, University of Lisbon, Portugal; [16]Newark Beth Israel Medical Center, Newark, New Jersey, United States; [17]Children's Hospital Colorado, Aurora, Colorado, United States; [18]Emory University School of Medicine, Atlanta, Georgia, United States; [19]McKusick-Nathans Department of Genetic Medicine, Johns Hopkins University, Baltimore, Maryland

Introduction and Objectives

- Achondroplasia, caused by a recurrent, gain-of-function mutation in the fibroblast growth factor receptor-3 (FGFR3) gene, leads to impaired endochondral ossification and is characterized by disproportionate short stature and significant medical complications[1,2]
- Vosoritide is a modified recombinant human C-type natriuretic peptide (CNP) analogue that leverages the CNP pathway to counteract overactive FGFR3 signaling and stimulate endochondral bone growth[3]
- In clinical trials, treatment with vosoritide has been shown to increase growth velocities in children with achondroplasia[4-6]
- Vosoritide is approved for use in children with achondroplasia and open growth plates aged ≥ 5 years in the United States (US), aged ≥ 2 years in the European Union (EU), Brazil and Australia, and from birth in Japan
- Here we present key clinical practice considerations for treating patients with vosoritide based on the collective early treatment experiences of clinicians across different institutions and regions in the EU and the US

Design and Methods

- Two meetings were held to gather insight and share knowledge among clinicians who have experience in using vosoritide in clinical practice
  - One meeting was held in Dublin in July 2022 and was attended by representatives from Europe (Austria, France, Germany, Portugal) and the Middle East (Saudi Arabia)
  - The second meeting was for participants in the US, and attendance was spilt over two days in September and October 2022
- The collective group comprised 10 geneticists (MB, RC, VCD, DD, MF, JHF, EL, SS, AT, WW), six pediatric endocrinologists (GH, KM, TR, OS, PS, AV), two paediatricians (JL, FR), and two orthopedic surgeons (AH, KW)
- The aims of the meetings were (1) to share knowledge gained through the early clinical experience of using vosoritide and (2) to discuss practical considerations for those wishing to incorporate vosoritide into their own practice

Results

- At the time of the meetings, the group was collectively managing >220 patients who were receiving vosoritide in clinical practice, aged 2–16 years
- Informed by their shared experience, the group identified practical aspects of management that should be considered by centers planning to initiate vosoritide treatment

Site preparation

Multidisplinary care team

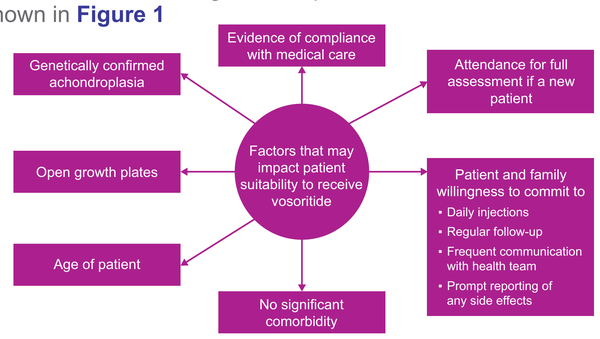
- Recent guidelines recommend that achondroplasia should be managed by an experienced multidisciplinary team (MDT) throughout the lifespan[7,8]
- The initiation of vosoritide should not replace the need for coordinated MDT management and follow up, nor constitute an extra barrier to its adequate implementation
  - MDT should ideally include genetics, endocrinology, neurology, orthopaedics, and specialist that can provide psychological support as a minimum

Infrastucture considerations

- Clinical capacity and accessibility to equipment and expertise to perform assessments (e.g. calibrated stadiometers/scales, Tanner staging, radiographic and laboratory tests)
- Logistics and storage arrangements for pharmacies and families
- Ability to understand and navigate the reimbursement landscape

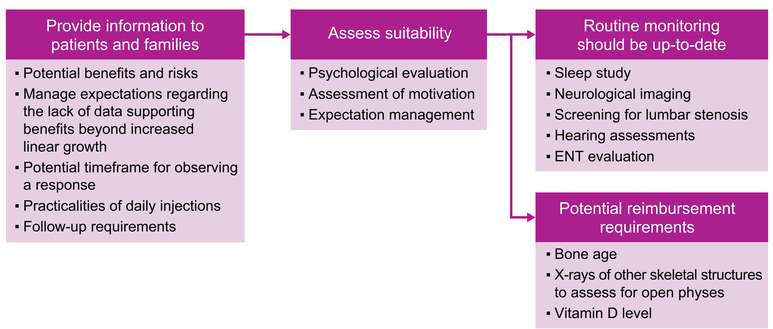
Patient selection criteria

- Considerations for selecting suitable patients for treatment with vosoritide are shown in **Figure 1**



Preparing for initiation of treatment

- **Figure 2** is an example of a clinic protocol to prepare for initiation of treatment. Protocols will differ between centers and regions and may be dependent on a number of factors including the healthcare system, available expertise, accessibility of equipment and testing capability



Addressing parental/caregiver concerns

Concerns can be due to

- Conflicting information
- Unknown long term safety in real world
- Potential change in physical appearance and self-identity
- Parents/caregivers making the decision on child's behalf

Parents and caregivers can be supported by

- Psychological support
- Continuous and easily accessible injection training and related support
- Information on practical aspects of daily injection: body site selection, pain management, creating a routine etc
- Sharing information about safety and efficacy in a fit-for-purpose way
- Information about common side effects and what to do in such cases

Clinical assessments

- **Table 1** shows core assessments that may be included in vosoritide follow-up protocols; these are in addition to routine monitoring that is performed as part of the management of children with achondroplasia

Assessment	Considerations	Timing				
		Day 0	Month 1	Month 3	Every 6 months	Annually
Treatment-informing assessments						
Parental height considerations		✓				
Tanner staging	May be a requirement of reimbursement authorities	✓			✓	
Bone age	May be an annual requirement of reimbursement authorities Clinicians may choose do less often (e.g., at baseline, then at signs of puberty)	✓				✓
X-ray	For assessment of growth plate closure	✓				✓
Vitamin D level	May be a requirement of reimbursement authorities	✓				✓
Efficacy assessments						
Anthropometrics	May include: ▪ Standing and sitting height ▪ Height ▪ Arm span ▪ Flexion and contractures ▪ Upper and lower arm segment ▪ May be a requirement of reimbursement authorities	✓			✓	
Annualized growth velocity	May be a requirement of reimbursement authorities				✓	
Symptoms (e.g., headaches, vision changes, worsening joint pain)			✓	✓	✓	
Safety assessments						
Review adverse events					✓	
Discussion of concomitant/new medications					✓	
Discussion of other interventions					✓	

Managing expectations

- Expectation management is vital to ensure patients and caregivers fully understand what might be achieved, and to establish the goals of treatment

Emphasize to patients and caregivers that treatment response to vosoritide can vary, and that a visible response to vosoritide treatment may not be immediately evident → Sharing patient's growth curve in comparison to achondroplasia-specific curves may be useful to demonstrate response and provide motivation to stay on treatment

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Although some reimbursement authorities may require a treatment response by 1 year, there is general agreement that a longer timeframe (2 years) may be required to better assess response

Treatment adherence, pause or discontinuation

- Providing ongoing support and training for patients and caregivers may minimize stress associated with the daily injections process and potential for non-adherence or discontinuation

Treatment pause can happen due to the burden associated with daily injections, life circumstances such as stressful situations, vacations or trips, or during surgical procedures → Parents/caregivers should be assured that final adult height might be affected, and there is a possibility of antibody production to start-stop approach to treatment, but there are no adverse health implications when pausing or discontinuing treatment with vosoritide

Treatment discontinuation can happen due to the burden associated with daily injections, inclusion in a clinical trial, or perceived lack of meaningful response →

Concomitant use with other treatments and procedures

- The multisystem complications of achondroplasia may lead to other interventions, such as ENT procedures or orthopedic surgeries, being required during the period in which a patient is receiving vosoritide
- There is currently no published evidence to either support or contradict the concomitant use of vosoritide with interventions to address the complications associated with achondroplasia

Counsel patients and caregivers on any potential contraindications, and discuss the pros and cons of pausing vosoritide treatment during other interventions

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The lead clinician as part of the wider MDT should provide the best available knowledge to the patient and their caregivers to support the decision-making process

Conclusions

- Vosoritide is a new treatment option for children with achondroplasia
- The sharing of early experience by providers treating children with achondroplasia is important and has proven useful in developing standards and guidelines for patients and families on vosoritide treatment

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