

Histrelin implant for the treatment of central precocious puberty

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Central precocious puberty is defined as puberty occurring prior to the age of 7.5–8 years in girls and 9 years in boys. The main goals of treatment include the arrest of pubertal progression and preservation of final adult height. In the USA, depot leuprolide has been the mainstay of treatment. It is a gonadotropin-releasing hormone agonist that is administered as an intramuscular injection every 4 weeks. Recently, a 1-year subcutaneous implant has been developed for continuous delivery of the gonadotropin-releasing hormone agonist histrelin. Initial prospective trials have demonstrated that it is efficacious, safe and well tolerated. It is an exciting alternative to painful monthly injections for the treatment of central precocious puberty.

Central precocious puberty (CPP) results from early activation of the hypothalamic–pituitary–gonadal axis. It is defined as puberty occurring prior to the age of 8 years in Caucasian girls, 7.5 years in African–American girls and 9 years in boys [1]. It occurs in one in 5000 to 10,000 children. The etiology of CPP varies by gender. In girls, it is most frequently idiopathic whereas in boys it is most commonly due to an organic cause such as tumor, trauma, radiation or other brain anomalies [2]. Children with CPP present with secondary sexual characteristics as well as accelerated growth velocity. While some have a slowly progressive form that does not require treatment, others experience rapid progression of pubertal development and skeletal maturation, therefore, these children appear taller than their peers, however, due to their advanced bone age, they have poor predicted adult heights [3]. The diagnosis of CPP is frequently confirmed by demonstrating elevated levels of leutinizing hormone (LH) and follicle-stimulating hormone (FSH) in response to gonadotropin-releasing hormone (GnRH) stimulation, or measured randomly using ultrasensitive assays.

Overview of the market

The main goal of the treatment of CPP is to slow down skeletal maturation and preserve final adult height [4]. Since the mid-1980s, the treatment of choice has been long-acting GnRH agonists (GnRHa) [5]. Paradoxically, continuous stimulation of the pituitary gland by GnRHa, as opposed to the pulsatile secretion normally seen in puberty, downregulates the GnRH receptors and inhibits gonadotropin release. This leads to suppression of the entire hypothalamic–pituitary–gonadal

(HPG) axis [6]. Several types and modes of delivery of GnRHa are available for the treatment of CPP in children. These include, in order of increasing potency, leuprolide, buserelin, deslorelin, nafarelin and histrelin [7]. The routes of administration vary and include multiple daily intranasal applications, daily subcutaneous injections and monthly intramuscular depot injections. The latter ensure better compliance and, therefore, are preferred for most patients. A 3-month depot leuprolide formulation is also available and offers the advantage of less frequent injections. However, a comparison study found that gonadotropin suppression is more pronounced with the monthly depot compared with the 3-month preparation [8]. In the USA, the most widely used US FDA approved agonist is depot leuprolide acetate, which is administered as a monthly intramuscular injection. It has been found to be extremely effective in suppressing the HPG axis at a dose of 0.2–0.3 mg/kg every 4 weeks [9]. It also improves predicted adult height compared with baseline in most children, although rigorous prospective controlled trials have not been performed. Factors that positively impact post-treatment final height include shorter duration of untreated precocious puberty, younger age and younger bone age at the start of therapy [10–13]. While depot leuprolide is extremely effective and has very few side effects (of which the most common is sterile abscesses), the monthly injections are painful and lead to decreased compliance. Once initiated, GnRHa therapy is typically continued for a minimum of 2 years and may be for as long as 8 years. Long-term follow-up, while limited, has thus far been reassuring in terms of reproductive function [14].

Keywords: central precocious puberty, gonadotropin-releasing hormone agonists, histrelin, implant

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Histrelin acetate is a GnRHa that is 210-times as potent as GnRH [15]. It has been available in the USA since 1991 and has been shown to be an effective treatment of CPP [16]. However, it has not been routinely used because it was only available as a daily subcutaneous or intranasal preparation, which makes it inconvenient and more likely to be ineffective secondary to noncompliance. However, recently, a histrelin subcutaneous implant that has been used successfully for the treatment of prostate cancer was studied in children with CPP [17–19].

Histrelin implant

The histrelin hydrogel implant is a flexible, nonbiodegradable, biocompatible device that contains histrelin acetate. It provides constant histrelin release by maintaining its shape and concentration gradient across its microporous walls. The water content of the hydrogel can be manipulated to provide a specific release rate [15]. The implant is 3.5 cm in length, 3.0 mm in diameter and has a wall thickness of 0.5 mm [20] (Figure 1). The implant used for the treatment of CPP contains histrelin acetate 50 mg and releases the drug at an average rate of 65 µg/day. It is inserted subcutaneously, and comes with a trocar specifically designed for its implantation (Figure 2).

Pharmacokinetics

The pharmacokinetics of the histrelin implant were studied in detail in 17 men (median age, 75 years) with advanced prostate cancer [15]. The implant was designed to release histrelin at a rate of 50 µg/day over a 1-year period, since suppression of the HPG axis requires less drug in aging males with prostate cancer than in children with CPP. In the majority of patients, histrelin concentrations were detectable within 5 min of insertion of the implant. Peak histrelin concentration was 1.1 ng/ml and was achieved at a median of 12 h, with a range of 6 h to 36 weeks.

The implant delivered histrelin continuously over the next 52 weeks with slowly declining serum concentrations. Mean histrelin concentration over the 52-week period was approximately 0.265 ng/ml. At the end of the study, the explanted device was analyzed for residual drug, and based on that the mean rate of release was determined to be 56.7 ± 7.71 µg/day, which is quite close to the rate it was designed to deliver.

Pharmacokinetic data in pediatrics is also available but is not as extensive. In a Phase III study of 36 patients, histrelin concentrations were analyzed throughout the 12-month trial. As in the adult data, serum concentrations of histrelin were sustained throughout the 1-year study period, with concentrations highest at 1 month and decreasing gradually over the course of the year. Total exposure to histrelin was approximately a third higher for the implant used for CPP versus the implant used for prostate cancer. The median maximum plasma concentration over the study period was 0.43 ng/ml, which is expected to maintain gonadotropin suppression. A subset of five children underwent additional pharmacokinetic sampling, which indicated an initial increase in histrelin concentration beginning 6–8 h after implantation [20].

Clinical trials

Two prospective studies investigating the use of the histrelin implant for the treatment of CPP have been conducted. The first was a Phase II pilot study of 11 girls aged 2–9 years [21]. All girls had physical as well as biochemical evidence of CPP and all had been previously treated with a depot intramuscular GnRHa. The implant was left in place for 15 months in six of the girls and 9 months in the remaining five. The investigators found that rates of bone age advancement, as well as growth velocity, significantly decreased in all subjects, and that breast development regressed. LH and estradiol concentrations were significantly decreased compared with preinsertion values in response to histrelin.

Due to the encouraging findings of this pilot study, a Phase III, multicenter, prospective trial was then performed to further evaluate the safety and efficacy of the histrelin implant [20]. A total of 36 subjects (three boys) were enrolled in the study; of these, 20 patients were treatment naive and the rest had been treated with standard GnRHa therapy for at least 6 months prior to study entry. Unlike in the pilot study, the insertion technique was standardized and a trocar device was designed for the implant insertion. All

Figure 1. Histrelin implant

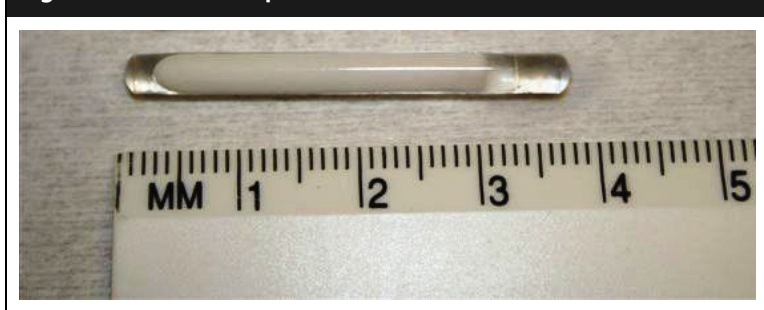


Figure 2. Trocar for implant insertion.



was 0.6 ± 2.3 and -1.8 ± 2.5 in the naive and previously treated patients, respectively. Predicted adult height did not differ significantly at the end of 12 months compared with baseline. Key findings from each of the two trials are summarized in Table 1.

Safety & tolerability

Both studies showed that the histrelin implant was generally safe and well tolerated. Of the patients in the multicenter study, 50% reported minor discomfort from pain and bruising at the insertion site that resolved without therapy within 2 weeks.

One patient in the pilot study developed a minor local infection at the site of the implant that was successfully treated with antibiotics. Spontaneous extrusion of the implant occurred in the pilot study in one patient 6 weeks after insertion, whereas no episodes of extrusion occurred in the Phase III study in which the trocar was used. The major difficulty was in implant removal. In seven cases, the implant broke during the removal process. One case required ultrasound localization of the implant prior to removal. Further studies are required to determine if difficulty with implant removal is a common occurrence. Although the scar at the site of the implant is typically extremely mild, three children did experience keloid formation. No other adverse events were identified, and no patient withdrew from either study as a result of adverse events.

procedures were performed by pediatric surgeons; however the type of anesthesia was left up to the discretion of the individual institution and, thus, differed accordingly. Two centers used local anesthesia with distraction, four used conscious sedation and three used general anesthesia.

By 1 month following implantation, peak stimulated LH decreased significantly compared with baseline levels in both the naive and previously treated patients. LH levels remained suppressed in all patients throughout the 12 months of the study (Figure 3). Similarly, testosterone levels in boys and estradiol levels in girls remained suppressed throughout the study. The bone age:chronological age ratio decreased significantly in all subjects. At the end of the study, growth velocity standard deviation score

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Figure 3. Leutinizing hormone suppression over time.

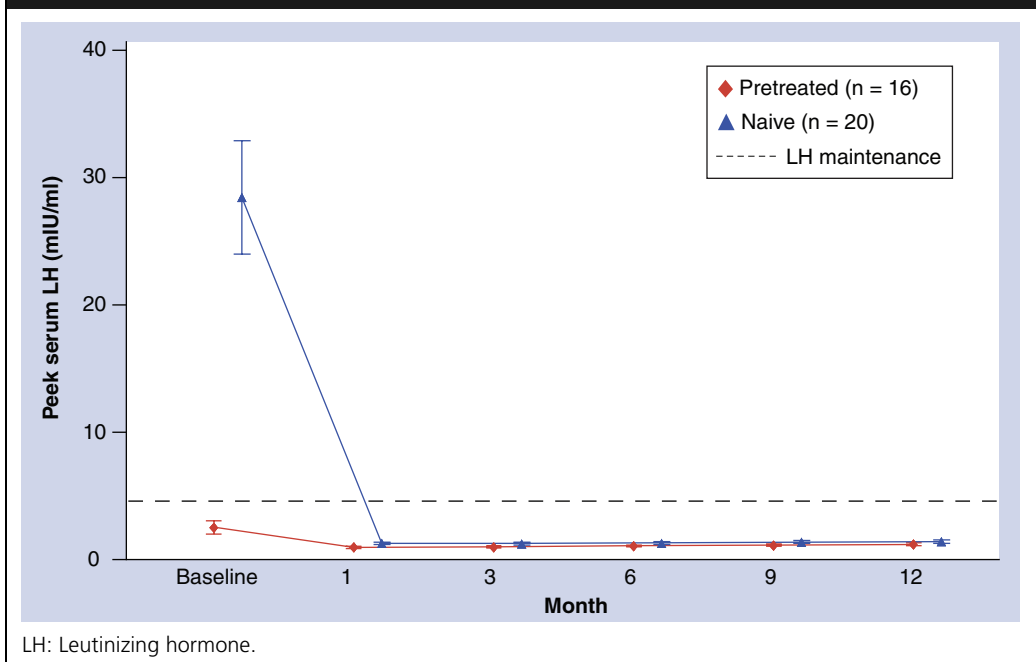


Table 1. Key findings of two clinical trials of the histrelin implant.

Study (year)	n (boys) treatment status	Age range (years)	Duration of therapy (months)	Results: efficacy	Results: safety	Ref.
Hirsch <i>et al.</i> , (2005)	11 (0) previously treated	8.5 (3.75–11)	15 (n = 6) 9 (n = 5)	Peak LH decreased from 1.3 ± 1.34 mIU/ml to 0.2 ± 0.06 mIU/ml (p < 0.01) E ₂ decreased from 9.83 ± 6.39 pg/ml to 6.52 ± 4.02 (p < 0.05) BA/CA decreased from 1.7 ± 0.5 to 0.6 ± 0.4 (p < 0.003) GV SDS decreased from 2.5 ± 1.7 to -3.1 ± 2.2 (p < 0.005)	Minor local infection (n = 1); implant extrusion (n = 1)	[21]
Eugster <i>et al.</i> , (2007)	36 (3) 20 naive, 16 previously treated	7.9 ± 1.7 (4.5–11.6)	12	Peak LH decreased from 28.2 ± 19.97 mIU/ml (naive) and 2.1 ± 2.15 (pre-Rxed) to 0.8 ± .39 mIU/ml and 0.5 ± 0.32 by 1 month (p < 0.0001) E ₂ decreased from 24.5 ± 22.27 pg/ml (naive) to 5.9 ± 3.7 (p = 0.0016) BA/CA decreased from 1.4 ± 0.2 to 1.3 ± 0.1 (p < 0.0001)	Mild implant site reactions (n = 18); difficulty with implant removal (n = 7)	[20]

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Normal ranges: LH (prepubertal) <1.0 mIU/ml, E₂ (prepubertal) < 20 pg/ml.

BA/CA: Bone age:chronological age ratio; E₂: Estradiol; GV: Growth velocity; LH: Leutinizing hormone; SDS: Standard deviation score.

Patients reported less pain and discomfort with the implant as compared with the monthly depot injections, although this information was formally collected only in the Phase II study. At the conclusion of the Phase III trial, all but one of the 32 children continued on GnRHa opted to have a second implant placed, and 22 of these have subsequently gone on to have a third. sex-steroid production. Bone age advancement as well as growth velocity decreased significantly in all subjects. The reported adverse events were minor, and were related to the mechanical aspects of the implant, particularly its removal. None of the events caused patients to withdraw from the study. In summary, the implant has been shown to be efficacious, safe and well tolerated.

Regulatory affairs

The 1-year histrelin implant was approved by the FDA for the treatment of CPP in May 2007 under the trade name Supprelin® LA (Indevus Pharmaceuticals, Inc., Hauppauge, NY, USA). It has not yet been approved in Europe or elsewhere.

Conclusion

Gonadotropin-releasing hormone agonists for the treatment of CPP have been the standard of care worldwide for approximately 20 years. However, in the USA, treatment of CPP has traditionally involved painful monthly injections. The advent of a novel approach that provides continuous delivery of GnRHa in the form of the histrelin implant is an exciting new alternative. Two prospective trials have examined its use in children with CPP. In both studies, the implant demonstrated profound suppression of gonadotropin and

Future perspective

Since the histrelin implant is a newly approved treatment option for children with CPP, there are several issues that deserve consideration. The implant is slightly more expensive than standard therapy and this may have implications in terms of insurance coverage. Another issue is implant insertion. While it comes with an insertion kit and instructions, the reported difficulties with removal and the risk of breakage may discourage nonsurgical physicians from performing the implantation, resulting in additional costs being incurred from a surgical referral. In addition, potential benefits should be balanced against the risks of general anesthesia, should this method be utilized. Finally, the results currently available are from a relatively short duration.

While the 1-year data are encouraging, questions regarding long-term safety related to the greater potency of histrelin remain. Whether

Executive summary

- Central precocious puberty (CPP) is defined as puberty occurring prior to the age of 8 years in girls and 9 years in boys.
- Gonadotropin-releasing hormone agonists (GnRHa) constitute the mainstay of treatment. Depot-leuprolide, in the form of intramuscular monthly injections, has been most commonly used in the USA.
- Recently, a 1-year implant has been designed for continuous delivery of histrelin, another GnRHa. It has been used successfully in men with prostate cancer.
- Two prospective trials have examined the use of this implant for the treatment of CPP. The implant was found to deliver histrelin continuously over the course of the year. In both studies, it was effective in suppressing gonadotropins and sex steroids and in slowing down growth velocity.
- The implant was found to be safe and well tolerated. The main side effects included mild local reactions at the site of the implant as well as difficulties with implant removal.
- The histrelin implant constitutes an exciting alternative to monthly injections in the treatment of CPP. Future studies are needed to examine long-term effects.

the profound suppression of the HPG axis caused by histrelin will translate into adverse effects in terms of its reversibility and impact on growth velocity, bone mineralization and future fertility are unknown. Finally, whether efficacy can be maintained by a single implant for longer than 1 year in some children is similarly unclear. Ongoing studies are needed to confirm the initial promising results of this new strategy for the treatment of CPP.

Financial & competing interests disclosure

Erica Eugster serves on an Advisory Board for Indevus pharmaceuticals and participates in clinical trials sponsored by Indevus.

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