The Rationale and Design of TransCon GH

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BACKGROUND

With growth hormone (GH) receptors on virtually all cells, GH replacement therapy should achieve the same tissue distribution and effects as endogenous GH. Thus, the fundamental challenge of developing a long-acting growth hormone (LAGH) is to create a more convenient GH dosing profile while retaining the same excellent safety, efficacy, and tolerability of daily human growth hormone (hGH), including maintaining GH and resulting IGF-1 levels within the physiologic range.

To create a LAGH that extends the GH half-life thereby allowing less frequent dosing, two basic approaches have been followed: (a) combine unmodified GH with a prolongation technology (a depot, crystal, or prodrug) or (b) modify GH in such a way (protein enlargement or albumin binding) that the GH analogue has a longer half-life.[1] TransCon GH, designed to release unmodifed GH, is therefore expected to have the same tissue distribution and receptor activation as daily GH.

METHODS

We reviewed LAGHs that have reached various stages of clinical development, categorized them by development approach, and evaluated their status for the indication, pediatric growth hormone deficiency (GHD).

RESULTS

Four LAGHs have been developed in which GH half-life extension was achieved by combining unmodified GH with a prolongation technology. Ten LAGHs have been developed in which GH half-life extension was achieved by modifying GH such that its molecular size was increased (or modified with high affinity albumin).

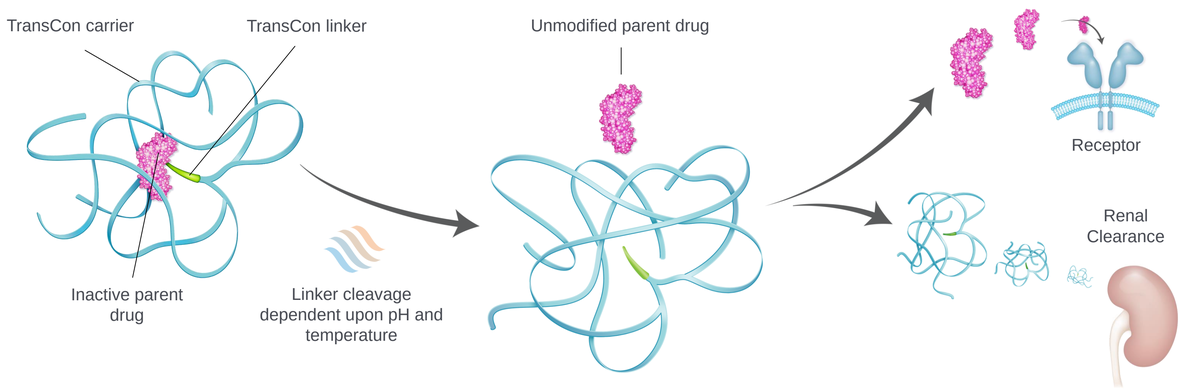
Approach		Company	Product	Design	Pediatric GHD Development Status
Unmodified GH	Half-life extension achieved by the slow-release of somatropin from polymeric depot, crystal, or prodrug	Genentech, Inc.	Nutropin Depot	GH encapsulated in polylactide-coglycolic acid microparticles	Approved in the U.S; later withdrawn
		LG Life Sciences, Ltd.	LB03002	GH encapsulated in sodium hyaluronate microparticles	Approved but not marketed in Europe; available in South Korea
		Altus Pharmaceuticals, Inc.	ALTU-238	GH crystallization	Discontinued
		Ascendis Pharma A/S	TransCon GH	Transiently PEGylated GH prodrug	Phase 3
Modified GH	Half-life achieved by increasing molecular size (except NNC0195-0092, which is modified with a small albumin affinity tag)	GeneScience Pharmaceuticals Co., Ltd.	Jintrolong	Permanently PEGylated GH	Available in China
		Pfizer, Inc.	PHA-794428	Permanently PEGylated GH	Discontinued
		Novo Nordisk A/S	NNCl126-0083	Permanently PEGylated GH	Discontinued
		Ambrx, Inc.	ARX201	Permanently PEGylated and mutated GH	Discontinued
		Teva Pharmaceutical Industries, Ltd.	TV-1106	GH fused to albumin	Discontinued
		Versartis, Inc.	VRS-317	GH fused to XTEN	Discontinued
		OPKO Health, Inc.	MOD-4023	GH fused to carboxyterminal peptides	Phase 3
		Novo Nordisk A/S	NNC0195-0092	Mutated GH attached to an albumin affinity tag	Phase 2
		Genexine, Inc., and Handok, Inc.	GX-H9	GH fused to an Fc fragment	Phase 2
		Hanmi Pharmaceutical Co., Ltd.	LAPS-rhGH/HM10560A	GH fused to an Fc fragment	Phase 2

Of these 14 LAGHs, only 2 have been approved by either the Food and Drug Administration (FDA) or the European Medicines Agency (EMA); both released unmodified GH, thus presumably replicating distribution and pharmacological actions of daily GH.

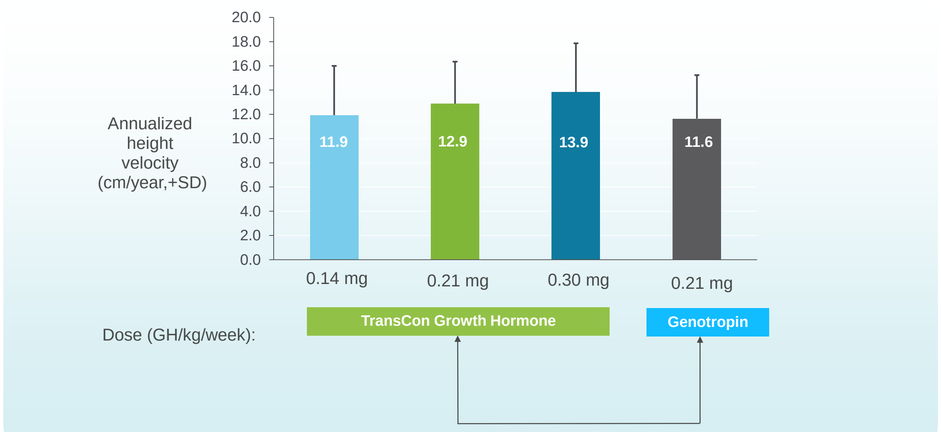
In contrast to LAGHs that release unmodified GH, 5 of the 10 LAGHs that modify GH have been discontinued. Problems associated with modified GH configurations included lipoatrophy, inadequate IGF-1 profiles, supraphysiologic GH levels, neutralizing antibodies, inadequate HV, and failure to normalize body composition.

TRANSCON GH

TransCon GH is a LAGH prodrug in phase 3 development in which GH is transiently bound to an inert carrier. It was designed to sustainably release unmodified GH over 7 days to achieve the same safety, efficacy, and tolerability as daily GH but with more convenient weekly dosing.



In a phase 2 trial of children with growth hormone deficiency (GHD),[2] similar safety, efficacy and tolerability to daily GH was shown. IGF-1 standard deviation scores (SDS) increased into normal range. Annualized height velocity (HV) was not statistically different from daily GH. Anti-drug antibody formation (immunogenicity) was low and comparable to daily GH, with no neutralizing antibodies.



The mean body mass index SDS was stable, similar to daily GH. Adverse events were mild to moderate without lipoatrophy, also comparable to daily GH. Data from the phase 3 heiGHt Trial in pediatric GHD is expected in 2019.

DISCUSSION

From fish to humans, GH is highly conserved across species, ranging from 19.4 to 22 kDa in size; studies have suggested that molecules larger than 40kDa may have difficulty diffusing through a murine growth plate.[3] This suggests evolutionary constraints on the functional GH molecule and the importance of size in maintaining natural tissue distribution.

Based on the physiology of GH and IGF-1 (and their interplay), unmodified GH may distribute more fully into peripheral tissue whereas protein-enlarged GH molecules may have restricted access, leading to an imbalance in GH and IGF-1 with subsequent unintended consequences.

CONCLUSION

The only LAGHs that have succeeded in replicating both accelerated HV as well as improvement of metabolic profiles observed with daily GH have been formulations that release unmodified GH. A viable LAGH would likely have to maintain the same tissue distribution as endogenous GH, ie, a candidate based on unmodified GH.

REFERENCES:
[1]Sprogoe, K., et al., *The rationale and design of TransCon Growth Hormone for the treatment of growth hormone deficiency.* Endocr Connect, 2017. 6(8): p. R171-r181.
[2]Chatelain, P., et al., *A Randomized Phase 2 Study of Long-Acting TransCon GH vs Daily GH in Childhood GH Deficiency.* J Clin Endocrinol Metab, 2017. 102(5): p. 1673-1682.
[3]Farnum, C.E., et al., *In vivo delivery of fluoresceinated dextrans to the murine growth plate: imaging of three vascular routes by multiphoton microscopy.* Anat Rec A Discov Mol Cell Evol Biol, 2006. 288(1): p. 91-103.

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