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Sermorelin: A better approach to management of adult-onset growth hormone insufficiency?

Growth hormone replacement therapy (GHRT) using recombinant human growth hormone (rhGH) has been embraced by many age management practitioners as one of the most effective methods for opposing somatic senescence currently available. However, its routine use has been controversial because few clinical studies have been performed to determine the potential risks of long-term therapy. Also, certain medical and legal issues have not been resolved causing some practitioners to restrict their use of the product. Some of these issues include the fact that:

- Improper dosing can lead to side effects that may be serious in some patients,
- Injection of hGH creates unnatural conditions of exposure to the hormone that may erode normal physiology,
- The Code of Federal Regulations specifically forbids the use of rhGH in adults except for treatment of AIDS or human growth hormone deficiency (GHD) diagnosed pursuant to regularly accepted guidelines.

While there is a wealth of information showing that long-term administration of rhGH reduces intrinsic disease and extends life in adults suffering pathogenic GHD, consensus on whether extrapolation of those data to the aging condition is justified has not been reached (Perls et al 2005). Most of the major concerns derive from the fact that rhGH is mitogenic and may awaken latent cancers, that improper dose selection may promote metabolic disorders such as diabetes, and perhaps that pharmacological presentation may exacerbate decline of endocrine function by distorting essential hormonal interactions. Of course, all these concerns are speculative and will not be resolved until sufficient scientific evidence for or against GHRT eventually accumulate. In the interim, the value of rhGH in GHRT will continue to be debated; unfortunately based more upon personal prejudice than objective information.

Despite the eventual outcome to the "Great Hormone Debate" as it has been titled in media articles (Landsmann 2006), certain negative aspects of GHRT using rhGH cannot be disputed and justify searching for a better alternative. For example, "square wave" or pharmacological presentation of the exogenous hormone cannot be avoided since it is administered as a bolus, subcutaneous injection. Since the amount of rhGH entering the general circulation is not controlled by normal feedback mechanisms, tissue exposure to elevated concentrations is persistent and eventually may lead to tachyphylaxis and reduced efficacy. Also, because the body cannot modulate tissue exposure to rhGH, the practitioner is required to "best guess" the appropriate dosage based upon little other than serum measurements of insulin-like growth factor-1 (IGF-1) and subjective comments from the patient about perceived responses to the hormone. Thus, it would seem that an alternative method(s) of GHRT that circumvented these problems would be of great value so long as it retained the positive attributes of rhGH.

One possibility that is receiving growing attention is the use of GH secretagogues to promote pituitary health and function during aging. An example of such molecules is growth hormone releasing factor 1-29 NH_2-acetate, or sermorelin, that recently became available to practitioners for use in longevity medicine (Merriam et al 2001). Other alternatives include orally active growth hormone-releasing peptides

that are currently being developed by pharmaceutical companies. Some of these have been reported to be effective at improving physical performance in the elderly (Fahy 2006). However, it is unlikely that they will be marketed for several years. On the other hand, sermorelin, an analog of naturally occurring growth hormone-releasing hormone (GHRH) whose activity declines during aging, may presently offer a more immediate and better alternative to rhGH for GHRT in aging (Russell-Aulet et al 2001). The molecule was commercially produced and marketed for many years as an alternative to rhGH for use in children with growth retardation, but it could not compete with rhGH and was withdrawn as a therapeutic entity by the manufacturer. Paradoxically sermorelin failed as a growth-promoting agent in children for the very reason that it is a better alternative for GHRT in aging adults. Growth-deficient children need higher doses of growth hormone than can be achieved by stimulating production of their own hormone, whereas the beneficial effects of sermorelin on pituitary function and simulation of youthful growth hormone secretory dynamics in aging adults have little effect on growth rate in children. Unlike exogenous rhGH that causes production of the bioactive hormone IGF-1 from the liver, sermorelin simulates the patients own pituitary gland by binding to specific receptors to increase production and secretion of endogenous hGH. Because sermorelin increases endogenous hGH by stimulating the pituitary gland, it has certain physiological and clinical advantages over hGH that include:

- Effects are regulated by negative feedback involving the inhibitory neurohormone, somatostatin, so that unlike administration of exogenous rhGH, overdoses of endogenous hGH are difficult if not impossible to achieve,
- Because of the interactive effects of sermorelin and somatostain, release of hGH by the pituitary is episodic or intermittent rather than constant as with injected rhGH.
- Tachphylaxis is avoided because sermorelin-induced release of pituitary hGH is not "square wave", but instead simulates more normal physiology,
- Sermorelin stimulates pituitary gene transcription of hGH messenger RNA, increasing pituitary reserve and thereby preserving more of the growth hormone neuroendocrine axis, which is the first to fail during aging (Walker et al 1994).
- Pituitary recrudescence resulting from sermorelin helps slow the cascade of hypophyseal hormone failure that occurs during aging thereby preserving not only youthful anatomy but also youthful physiology (Villalobos et al 1997).

Finally, there is the question of lawful practice. Unlike rhGH which has legal restrictions on its clinical use, the off-label prescribing of sermorelin is not prohibited by federal law. Thus, it can be carefully employed and evaluated by the practitioner to objectively determine whether it provides greater benefits with less risk to his/her patients. In support of this effort, the Society for Applied Research in Aging will be providing sermorelin free of cost on a competitive basis to practitioners willing to study its effects under protocol conditions and to report the outcomes in a peer-reviewed journal such as *Clinical Interventions in Aging*. Hopefully, through such efforts we can contribute to development of a paradigm for evidence-based GHRT in clinical age management.

For more information on this effort and to participate in the protocol, please contact sermorelin@dovepress.com.

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