Introduction: KIMS and ACROSTUDY Supplement

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Treatment with growth hormone (GH) in adults with growth hormone deficiency (AGHD) was approved by the European regulatory agency (EMEA), 15 years ago. Genotropin, recombinant human GH (Pfizer Inc.), received marketing authorization based on randomized clinical trials (RCTs) including several hundred patients treated with Genotropin for a maximum of a few years. Based on the success of KIGS (Pfizer International Growth Database), which is an observational survey (-ObS) of long term efficacy and safety of GH treatment in children and adolescents with various growth disorders, the company decided in 1994 to initiate a similar survey (-KIMS, Pfizer International Metabolic Database) of Genotropin treatment in AGHD. Since then 48 peer review papers have been published with interesting and important data from KIMS about various aspects of GH substitution in AGHD.

When KIGS was initiated, more than 20 years ago, by a small Swedish pharmaceutical company, the value of a post marketing surveillance study was challenged. Many pediatric endocrinologists considered it simply as a marketing tool of value only for the company, and that only- RCTs could contribute new knowledge about treatment interventions. However, during the last decade, ObSs have contributed substantially to evidence based medicine (EBM). It is now recognized that in EBM a rigid hierarchy of research design (double blind placebo controlled RCT, RCT without placebo, observational survey with concurrent controls, ObS with historical controls, case studies etc) might not be valid (-1). The limitations of RCTs are perhaps underestimated and the limitations of ObSs overstated.

Certainly randomization protects against at least some types of bias in observational studies such as enrolling patients with less severe disease. Horowitz et al have described methods to avoid „healthy users bias” in ObS as well as „restriction cohort design” by using intention to-treat strategy in the statistical evaluation (2). Another potential weakness of some ObSs is the risk of missing early adverse reactions when the majority of included patients have been treated with the drug of interest -for a long time prior to inclusion i.e. non-naïve patients (3). This is not a major issue in KIMS as 73% are naïve to growth hormone at the time of enrollment.
Weaknesses of many RCT protocols include the restriction of the sample of patients to a very homogeneous group, the intervention delivered being strictly controlled, and the outcome measured having a highly reproducible method of assessment. While these strict protocol design features produce high quality scientific results, they can impair the generalization of the study to routine clinical care. The conclusions may be less applicable to patients in the "real world" of clinical practice. Another weakness of many RCT is the short duration and use of surrogate variables instead of long-term outcomes, such as biochemical variables instead of cardiovascular deaths or bone mineral density instead of fracture rates.

An important paper was published 2000 by Concato et al (4). In a meta-analysis point estimates (and confidence intervals) of exposure-outcomes association were assessed in RCTs and in ObS with concurrent control subjects. Close to two million study subjects in 99 original articles were assessed in five clinical areas such as treatment of hypertension, BCG vaccination and mammography. The analysis showed that the odds ratios were remarkably similar for RCTs and ObSs in all five areas. And it was only among RCTs that individual trials reported results in opposite direction of the pooled estimate i.e. representing a paradoxical finding. The authors suggested that an ObS is more likely to include a broader representation of the at-risk population compared to a RCT. Based on a similar analysis, Benson and Hertz concluded "that there is little evidence that estimates of treatment effects in observational studies are either consistently larger or qualitatively different from those obtained in randomized clinical trials" (5).

Today most physicians, researchers and regulatory agencies appreciate ObSs as important additions to RCTs. So what are the strengths and weaknesses of an ObS? First of all it has the capacity to include more patients compared to a RCT because the inclusion and exclusion criteria are usually less rigid, and the enrollment period longer. As a consequence, the patients included are most likely more heterogeneous and therefore may be more representative of the population at risk. Such variability may
include patients being a mix of old and young, with different durations of the disease of interest, and with various co morbidities which may impact the outcomes being measured. Observational studies can include thousands of patients by pooling data from many investigators around the world; this can be particularly powerful if the disease in question is uncommon. Especially in a chronic rare disorder like AGHD-, an ObS might be the best method for gathering enough patients for interesting and robust sub group analyses. Almost all patients with AGHD who are prescribed Genotropin are allowed to be included in KIMS, the only exclusion criterion being a contraindication to GH treatment. The number of patients enrolled in KIMS is now over 30,000 from 28 countries. This provides an opportunity to detect uncommon adverse drug reactions, (potential side effects). In addition, it is possible to, describe national differences in diagnostic and treatment approaches AGHD. Over the years, interesting subgroups have been analyzed, resulting in publications regarding childhood onset AGHD (6), isolated GHD (7), GHD after treatment of Acromegaly or Cushing syndrome (8), and GHD associated with Sheehan syndrome (9). In this supplement there are eight papers with data from KIMS. Some of them can be considered as minireviews of topics of interest in the field of AGHD like Cardiovascular risk factors in hypopituitary GH-deficient adults by Verhelst and Abs and the paper about Quality of life (QoL) by Koltowska-Häggström et al. Other papers focus on what has been published from KIMS over the years. Some of the papers include new data never previously published from KIMS such as the interesting data about QoL in the contribution by Koltowska-Häggström, novel findings about the progression of isolated GHD to multiple pituitary deficiency by Klose et al. and the discussion by Brabant et al about regional differences in etiology, characteristics and biochemical diagnosis in AGHD.

ACROSTUDY was established in 2004, following the approval of Somavert® (pegvisomant) as a second line treatment of acromegaly. As pegvisomant is an antagonist of growth hormone receptor and thus represents a completely new mechanism of action, both the FDA and EMEA required patients to be monitored in an observational survey.
In the current supplement there are two papers based on the data from ACROSTUDY. In addition, a valuable contribution reviews the German Pegvisomant Observational Study (GPOS), which was a multicenter study initiated prior to the start of ACROSTUDY, but following the same protocol is included.

The article of Brue et al. discusses the structure of ACROSTUDY and the baseline characteristics of enrolled patients. The treatment effects as well as the safety profile in almost 800 patients enrolled in ACROSTUDY with a mean pegvisomant treatment of 3.3 years are described in the paper by Trainer. As might have been predicted, the rate of IGF-I normalization observed in ACROSTUDY was lower than 90% reported in the initial RCT. This observation is in line with the aforementioned differences between results of RCT and “real-life” data from ongoing clinical practice. The former deals with a selected cohort of patients, who is followed for a limited time and usually highly compliant, and the latter often includes patients with multiple morbidities, inadequate responders and poor compliers. Additionally, as discussed in the Trainer paper, one of the important reasons for lower efficacy than in the original RCTs could be inadequate dosing in this heterogenous group of patients.

In summary, observational studies provide clinical information regarding large groups of patients typical of those seen in clinical practice, reflect local customs and offer physicians complimentary information to that obtained from rigorous randomised controlled trials. Strengths include the large cohort size, which is particularly useful in rare disorders, the long enrolment period, and the opportunity to capture risks and benefits of a treatment that circumscribed, randomised controlled trials or individual physicians in practice will not discern. This Supplement will provide an interesting array of information about data that has been published over the 15 years of KIMS and the 5 years of ACROSTUDY, as well as adding newly analysed data to the medical literature.

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References

