Missed OPPORTUNITY: growth hormone therapy in adults with CKD

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The results of the largest, double-blind, placebo-controlled, multicentre, multinational randomized clinical trial (RCT) evaluating the effects of human growth hormone (hGH) on clinical outcome in 695 haemodialysed adults are published in this issue [1]. Designed to answer the important question whether hGH therapy might improve the notoriously poor survival in patients on dialysis, the OPPORTUNITY trial will enter the collective memory of the nephrology community as a paradigmatic case illustrating the unfortunate dependence of clinical pharmacological research on the short-term interest of industry sponsors.

The rationale

The hypothesis the authors set out to test was well founded by ample experimental and clinical evidence. Mortality in haemodialysis (HD) patients strongly correlates with indicators of low protein mass. Growth hormone (GH) has extensive protein anabolic effects [2, 3], which have been well documented in experimental uraemia [4], in several long-term trials in children [5, 6]—including a placebo-controlled RCT [7]—resulting in approval of hGH for the treatment of uraemic growth failure, and finally in several controlled small-scale trials in adult HD patients [8–11]. hGH increases muscle mass and bone mineral density, decreases fat mass and induces corresponding biochemical changes [12]. While these effects are promising and suggested that hGH might improve physical functioning and quality of life [11], the key efficacy criterion required by regulatory authorities to consider approving hGH for the treatment of protein-energy wasting in adult dialysis patients was the demonstration of a positive effect on patient survival. OPPORTUNITY was the first trial designed to address this hard end point.

‘Sudden death’ of an RCT in the making

In order to detect a clinically relevant 20% difference in long-term patient survival as significant, 2500 patients were required to be followed on hGH or placebo treatment for 2 years. To meet this challenging task, patients were planned to be enrolled in 23 countries during a 28-month period. After just 15 months, when 712 patients had already been randomized, the sponsor decided to prematurely terminate the trial because enrolment was slower than anticipated. Consequently, the median time on treatment in the 695 subjects exposed to hGH or placebo was only 16 weeks and no patient completed the 24-month observation period. As a result, the trial remained grossly underpowered to address the primary hypothesis, not to mention the nuisance caused to the almost 700 patients frustratingly exposed to trial conditions.

This deplorable failure raises several issues: First of all, why was enrolment slower than expected? One possible factor might have been that many patients were unwilling to enrol in a trial that offered a 50% chance of daily placebo injections for 2 years. It may be time to reconsider the design principles of long-term therapeutic trials in order to minimize the likelihood of being denied a potentially beneficial treatment by being randomized to a control arm. Furthermore, could it be that protein-energy wasting in patients on maintenance HD is less common than usually reported? Of note in this context, the patients enrolled in the trial, >50% of whom were diabetics, ranged in body mass index (BMI) from 16 to 70, with 35% being in the obesity range (BMI > 30). Perhaps reflecting the difficulty of finding overtly malnourished patients, hypoalbuminaemia (<40 g/L) was used as the sole inclusion criterion. With more stringent inclusion criteria, it would have been even more difficult to reach the number of eligible patients within an acceptable time frame.

However, the crucial question in this context is what can actually be considered an acceptable time frame for a large-scale RCT. In industry-driven trials, sponsors and investigators tend to have differing views on this issue. With the enormous running costs of multicentre trials in the era of Good Clinical Practice (GCP), any unanticipated prolongation of the trial period imposes a significant financial burden on the sponsor. However, the knowledge gained from well-powered RCTs and their tremendous impact on therapeutic practices should nearly always be worth the extra effort. As an example, when the ESCAPE trial...
[13], an investigator-initiated multinational RCT in children with chronic kidney disease (CKD), fell short of recruitment goals after 15 months of enrolment, additional sites were included and the enrolment target was reached with almost 2 years delay. When it became evident that a 3-year study period was too short to obtain clear results, the study duration was extended to 5 years. Almost 10 years after its launch, the trial eventually yielded highly relevant information that profoundly changed treatment practices. The ESCAPE Trial was initiated before the current RCT regulations and sponsorship rules were implemented; nowadays, independent investigator-driven large-scale long-term trials have become virtually impossible due to financial constraints. This development is in partial conflict with the regulatory authorities’ legitimate demand to study hard end points.

The unlucky fate of the OPPORTUNITY trial underlines the need for new approaches in pharmaceutical research to facilitate the feasibility of RCTs for patients, investigators and sponsors. Such approaches should involve research into innovative trial designs, a critical review of excessive regulations dictated by GCP standards, optimization of study protocols towards minimized patient discomfort and the development of private–public partnership programmes for shared cost coverage and decision making in clinical trials.

Potential pitfalls beyond underpowering

Although OPPORTUNITY was not given the chance to prove or disprove the efficacy of hGH in improving survival on dialysis, several design issues that potentially would have affected outcomes deserve comment as they might be useful for the planning of any future trials in this area. An important topic relates to dose selection. Despite the early termination of the trial, >170 patients received hGH for at least 6 months. Administered at a dose of 20 \(\mu\)g/kg/day, the drug induced a reduction in body fat but failed to increase lean body mass (LBM) significantly. This experience contrasts with the clinical experience with hGH in paediatric dialysis patients, where a visible increase in LBM is regularly observed. The 20-\(\mu\)g/kg dose was chosen based on results of a Phase II dose finding trial [11], which had shown significant increases of LBM with 20, 35 and 50 \(\mu\)g/kg in HD patients. In the same study, the lowest dose of hGH was unexpectedly associated with the greatest increase in serum albumin, albeit with the lowest increase in LBM. Since the differences were not significant, the investigators chose the lowest dose for OPPORTUNITY in an attempt to minimize the risk of adverse events. In earlier studies in adults, hGH doses of 4 IU/m\(^2\)/day, equivalent to 35 \(\mu\)g/kg, were used [8–11], which is close to the dose utilized in children with CKD. With that dose, mean IGF-1 serum levels rose from 213 to 348 \(\mu\)g/L and IGFBP3 from 5.6 to 7.1 mg/L [9], whereas in the OPPORTUNITY Trial, mean IGF-1 levels were only 179 \(\mu\)g/L and IGFBP3 levels 4.8 mg/L at the end of study. This amount of stimulation of active IGF-1 achieved with the lower dose might have contributed to suboptimal clinical results in this dialysis population, even more so since recent studies have shown that a marked reduction of bioactive IGF-1 occurs during HD [14]. Thus, it is possible that a higher dose of hGH would have yielded a more distinct nutritional benefit in the OPPORTUNITY trial.

Furthermore, the study could be criticized for relying on serum albumin as the only inclusion criterion. Since serum albumin in dialysis patients reflects fluid as much as the nutritional status, the specificity of this criterion in diagnosing protein-energy wasting is weak. The therapeutic potential of hGH in improving the survival of patients who are fluid overloaded rather than malnourished is questionable.

Another possible pitfall relates to the age and physical activity of the population studied.

Mean patient age was 62 years, with a wide range from 19 to 96 years. The action of hGH, a widely used drug for illegal anabolic doping, on muscle accretion is believed to depend on concomitant physical exercise. In children with CKD treated with hGH, spontaneous physical activity might be high enough to allow for the positive effects of GH treatment. In elderly dialysis patients, physical activity might be minimal. While exercise capacity was measured in the course of treatment, actual physical exercise programmes were not included in the trial protocol. It would be of interest to know whether the change in LBM and other nutrition parameters depended on age and/or the physical exercise level.

hGH: an anti-inflammatory, vasculoprotective drug?

There was no difference between hGH and placebo regarding adjusted death rate, cardiovascular death, time point of death or any cardiovascular event.

In patients with acromegaly, adverse cardiovascular effects such as ventricular hypertrophy, arrhythmias and increased arterial intima-media thickness have been reported; however, it is important to keep in mind that GH production in acromegalic patients is elevated 25- to 100-fold [15], whereas the daily hGH dose injected in CKD patients exceeds endogenous production only by a factor of 2–3. Administered at these usual pharmacological doses, hGH might even exert beneficial cardiovascular effects. The aforementioned hGH dose finding study [11] had first suggested that serum transferrin and serum high-density lipoprotein might be increased and plasma homocysteine reduced by GH treatment. These findings were confirmed in the OPPORTUNITY Trial.

GH is a hormone of the cytokine family, counteracting certain effects of inflammatory cytokines in vitro and in vivo. In this context, the finding that high-sensitivity C-reactive protein serum levels declined significantly is of considerable interest as it links for the first time experimental evidence to a potential clinically important anti-inflammatory action. Inflammation is believed to be one of the key mechanisms underlying vascular calcification and cardiovascular morbidity in uraemia. Once again, it would take long-term studies to clarify whether hGH treatment can contribute to the prevention of those complications.
Conclusions

The unfortunate fate of the OPPORTUNITY trial is a major drawback to the utilization of hGH therapy in adult dialysis patients. In view of the sound underlying concept, the promising short-term results and the notable secondary findings observed even in this underpowered trial, it remains to be hoped that hGH therapy will be given a second chance to demonstrate efficacy in improving patient survival and well-being on dialysis, ideally in a better defined clinical sample and with a more extended commitment of the industry sponsor.

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Conflict of interest statement. Ipsen and Pfizer are manufacturers of hGH competing with Novo Nordisk, the sponsor of the OPPORTUNITY trial. (See related article by Kopple et al. OPPORTUNITY™: a large-scale randomized clinical trial of growth hormone in hemodialysis patients. Nephrol Dial Transplant 2011; 26: 4095–4103.)

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