EDITORIAL

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Request for regulatory guidance for cancer cachexia intervention trials

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Rome was not built in a day. Likewise, if one considers the evolution of systemic anti-cancer treatment, it took decades to go from acceptance of any therapy at all to single agents achieving isolated tumour responses (without prolongation of survival) to the current use of combination regimens as adjuvant therapy to surgery. Such incremental progress has led to improved quality of life and eventually survival for patients with some types of cancer.

Cachexia and skeletal muscle wasting in cancer are significant clinical problems of high medical need for a large proportion of cancer patients and associated with very poor quality of life and very high mortality.[1,2] An effective treatment of a complex multifactorial syndrome such as cachexia will likely evolve from a series of steps of discovery and new interventions before a comprehensive multimodal strategy can be identified that improves patient's quality and quantity of life.[3]

There are reasons to be optimistic about the possibility that in the future, cachexia may be treated effectively. A number of drugs have already been developed that target key underlying mechanisms, namely, reduced food intake and altered metabolism and regulation of muscle mass, with the latter being split into pro-anabolic and anti-catabolic approaches. However, there is also some reason to be concerned because of the wide variability in current trial design, including different inclusion criteria, endpoints, analysis plans and the definition of best concomitant supportive care. Taken to the extreme, such differences in general approach have resulted in divergent opinions on what to consider a meaningful clinical endpoint by the European Medicines Agency (EMA) versus the US Food and Drug Administration (FDA). A result has been that in the clinical development programmes of some drugs, different endpoint assessments for American versus European regulatory authorities within the same trials using the same source data have been adopted. An example is the case of the POWER 1 and 2 trials testing the selective androgen receptor modulator enobosarm in patients with cancer suffering from muscle wasting.[4–6]

There has been a considerable influence from regulatory authorities on trial design. In the last 10 years, some regulatory authorities have consistently suggested that the design of randomized controlled trials testing treatments for cachexia should be aimed at demonstrating appropriate risk versus benefit, where benefit is defined as concomitant improvement in skeletal muscle mass (or lean mass) and relevant/meaningful physical function or improved survival. Whilst this is an admirable goal, from recent phase III trial results, this appears to be possibly unachievable with single modality interventions. Equally, it is not defined to whom the change is supposed to be 'meaningful': patient, caregiver, doctor, nurse or healthcare provider? The recent phase III trials of enobosarm used a co-primary end-point of lean body mass and stair climb power.[4–6] Based on the FDA agreed

co-primary responder analysis the trials failed to reach significance, principally because of lack of benefit in terms of the functional end point. In the responder analysis demanded by the FDA, an increase in performance of at least 10% for stair-climb power test was required for a patient to be considered to have benefited clinically [paper submitted]. Preventing a decline in performance was not considered in these analyses. In the analysis suggested by the EMA (which generally aims to assess clinically meaningful change regardless of direction), the same data were analysed using continuous data, and one of the two POWER trials may be considered successful, as both tests for change in lean mass and for stair-climb power showed significant changes over time. The two trials also had to be different, because of different background chemotherapy demanded in the inclusion criteria (i.e. taxane and non-taxane based). It is not clear, whether these are two trials in two orphan-type cancer indications (with different results), or are instead two trials in one indication with inconsistent results. It all depends on your approach to drug development (and maybe also on the regulatory body you talk to), but certainly it is a confusing situation by any standard.

Similarly, the phase III (ROMANA) trials of the ghrelin receptor agonist anamorelin have shown significant benefit in terms of lean and fat body mass, but not for hand grip strength.[7] These findings are not completely unexpected since whilst in healthy young individuals there is a strong positive correlation between muscle mass and muscle strength/power *per se* and between changes thereof,[8,9] in older, sick individuals, the magnitude of strength generated by a certain unit of mass tends to be lower. These findings suggest that preservation/augmentation of muscle mass does not necessarily always translate into clinical benefits in non-muscular aspects of the cachexia syndrome as other factors may remain unchanged from a unimodal approach (e.g. targeting muscle anabolism). If other aspects of the cachexia syndrome remain unchanged (like systemic inflammation and catabolism or physical inactivity and undernutrition), can unimodal approaches lead to an increase in physical activity and/or preservation of independence? It appears that a more comprehensive approach to the cachexia syndrome is warranted if the reference outcomes of improved physical activity/preservation of independence are to be pursued. Still, preservation of function (and not its improvement) may also be a laudable aim of treatment development in cachexia, and regulatory guidance should permit for that. However, unlike areas such as hypertension where a given change in blood pressure is accepted as a surrogate for clinical events, it has to be recognized that in cachexia, the 'relevance' or 'meaningfulness' of a change in surrogates such as hand grip strength, stair-climb power, leg extension strength or timed sit-up-and-go is not known. Perhaps direct measures of patients' daily physical activity would be better?

In the related field of COPD-associated body wasting, exercise rehabilitation is well established with extensive guideline recommendations that are evidence-based.[10] These guidelines have been developed over time and are multimodal in focus and are explicitly aimed at improving physical functioning and physical activity levels, nutritional status and quality of life. For patients with heart failure, chronic kidney disease, stroke or ageing-related frailty, such multimodal approaches are frequently considered,[11–13] but evidence is so far weak compared with what has been achieved in COPD. Novel therapeutic agents under development for cachexia mostly focus on specific aspects of the syndrome (e.g. muscle anabolism, inflammation or appetite stimulation).[14] Surely, phase III registration trials should assess safety in general, but efficacy specifically in relation to the target of the drug based on its mechanism of action. It may not be right to discard an intervention as ineffective because it does not yet affect a functional outcome, if, in fact – when inserted into a multimodal intervention that reflects the multifaceted aspect of the cachexia syndrome – the drug shows extended benefits that touch on issues such as health-related quality of life, patient-reported symptoms and tolerance of anti-cancer therapy.

In the context of a complex disease process and a desire for multimodal therapies, regulatory advice on co-therapy with nutrition and exercise is also needed. Suggestions as to how best to include in this context supportive care in clinical trials [15] may also be helpful. We understand that this may include additional clinical trials for food products and supportive care approaches and surely this is acceptable, if the rules of the 'game' are clear for the good of our patients. Regulators need to be engaged in encouraging the testing of these modalities and their systematic inclusion in trial designs. In heart failure, such activities have already been initiated and aim to shift the development and authorization of medicines from the molecule paradigm to their evaluation in the context of the whole healthcare regimen.[16] If a trial of a new agent incorporates these elements and is successful, it cannot lie with the pharmaceutical company to ensure that such adjuncts are available in precisely the same format everywhere in the world. Rather, the approved drug label may need to recommend such adjuncts for optimal effect.

Clearly, this is not an easy field for new developments, but the medical need is great and the commercial returns for those who make it may be big. Once drugs are approved, the longer process of incorporating new agents into best clinical practice can begin. It should be clear to pharmaceutical companies, academic trialists and regulators that they may need to be more realistic about what can be achieved in a single step. Maybe also the adaptive licensing approach proposed by EMA [13] can help in this process of developing regulatory pathways.

A willingness to consider current data with an open mind and a 'Notice on Regulatory Guidance' on cachexia

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trial design for cancer and beyond that cuts across continents would be a major step forwards to maintain drug development momentum, if there is to be genuine progress at this exciting juncture in the development of cachexia therapy. We want to help make that a reality whichever way we can.

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