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ORIGINAL ARTICLE

Physical frailty and sarcopenia (PF&S): a point of view from the industry

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Abstract We have observed over the last 15 years a wide debate both in the medical scientific community and in the public health arena on the definition and operationalization of frailty, typically a geriatric condition, and in particular of physical frailty linked to sarcopenia. Because physical frailty in its initial phase can still be reversed, fighting sarcopenia in elderly persons has the potential to slow or halt progressive decline towards disability and dependency. Quite recently, regulators focused attention on frailty as an indicator of biological age to be measured to characterize elderly patients before their inclusion in clinical trials. A European guidance regarding most adapted evaluation instruments of frailty is currently under public consultation. Does the regulatory initiative imply we should now consider frailty, and particularly physical frailty, primarily as an important risk factor for adverse events and poor response, or mainly as a clinical tool helping the physician to opt for one therapeutic pathway or another? Or is physical frailty above all a specific geriatric condition deserving an effective and innovative therapeutic approach with the objective to curb the incidence of its most common result, e.g., mobility disability? Pharmaceutical industry developers consider both faces of the coin very relevant. We agree with regulators that better characterization of subpopulations, not only in elderly patients, can improve the benefit risk ratio of medicines. At the same time, we believe it is in the public health interest to develop novel drugs indicated for specific geriatric conditions, like osteoporosis in the 1990s and sarcopenia today. We consider it an important therapeutic goal to effectively delay mobility disability and to extend the active, independent, and healthy life years of aging people. The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) collaborative project under IMI is paving the way for adapted methodologies to study the change of physical frailty and sarcopenia in at-risk older persons and to adequately characterize the population that needs to be treated.

Keywords Aging · Geriatrics · Frailty · Sarcopenia · Active and healthy life

Introduction

Although sparse publications on "frailty" date from the early 1970s, it is after Fried's 2001 seminal paper [1] on the definition and operationalization of frailty as a specific geriatric syndrome that a wide debate rose in the medical scientific community around the concepts of frailty and sarcopenia. This discussion extended to the public health arena few years later regarding frailty as a predictor of dependence and death [2] not exclusively in high- or middle-income countries [3].

Frailty is an independent cause of death, primarily leading to progressive or persistent disability and not systematically overlapping with multimorbidity [2, 4]. Sarcopenia, a decline in skeletal muscle resulting from excessive muscle breakdown with insufficient muscle building, is an essential component of physical frailty [5–7]: frailty has been suggested a common final pathway of sarcopenia, although several impaired mechanisms of homeostasis characterize frailty and generate its propensity to negative outcomes

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[8]. Because physical frailty in its initial phase is partially reversible, the clinical interest in fighting sarcopenia is that the progressive decline toward physical disability can be slowed or halted.

Since 2006, regulators brought more attention to frailty as an indicator of biological age to be considered at the moment of including (or not) elderly patients in clinical trials for evaluating the safety and efficacy of novel treatments (for any disease). A guidance over baseline characterization of frailty in clinical trials populations is currently under public consultation [9].

Therefore, should we consider frailty, and particularly physical frailty, mainly as a risk factor for adverse events and poor response? Or is physical frailty a specific geriatric condition deserving an effective and innovative therapeutic approach to limit the incidence of its most common result, e.g., mobility disability?

In the current version of the European Medicines Agency's (EMA) "Points to consider on frailty: evaluation instruments for baseline characterisation of clinical trials populations", Short Physical Performance Battery (SPPB) [10] and gait speed at the usual pace [11] are proposed as reference assessment tools for physical frailty as stratification factor for increased vulnerability of the older person, and as predictive of adverse events in any clinical setting. Therefore, while these instruments integrate known and unrecognized disturbances in multiple organ systems, it is indirectly acknowledged that the loss of muscle strength is a key component of physical frailty clinical manifestations.

As many geriatric conditions, physical frailty linked to sarcopenia is underdiagnosed [12] and when recognized may remain untreated, confounded with "normal" aging. Conversely numerous guidelines were generated recommending adapted nutritional intake and structured physical exercise as available "treatments" to counteract the decline of muscle mass and function.

Although the EMA has progressively implemented specific policies aimed to improve the regulatory evaluation of medicines for older persons and to make the information about the benefit risk in the geriatric population more detailed [13–16], the regulatory recognition of geriatric indications, necessary to developing and marketing specific pharmacological treatments, remains undeveloped.

Interestingly, a novel opportunity arose in December 2010 to reignite the public health debate about how specific geriatric conditions are appraised and treated, when the European Commission launched a public consultation on adapted policies for promoting Active and Healthy Ageing actions across all countries in the European Union, with the aim of extending "active and healthy years" life expectancy while decreasing healthcare expenses linked to ineffective use of resources. A report summarizing the recommendations of stakeholders is published online [17].

Of note, during the Active and Healthy Ageing European Innovation Partnership (AHA-EIP) public debate, key regulatory gaps have been identified that hamper practical initiatives for developing innovative therapeutics for geriatric indications, starting from the lack of specific regulatory guidance for geriatric conditions. In fact, the categorical classification of diseases, which is the basis of the current regulatory science conceptual approach for developing and evaluating new medicines, appears no longer adequate to tackle the complexity of geriatric patients.

Subsequently, as a practical follow-up, the AHA-EIP was started to facilitate and streamline the scale-up of good practices on three main lines of intervention as presented in their strategy report, one of this concerning prevention of falls and early diagnosis of geriatric conditions like frailty or pre-frailty:

Pillar 1: prevention, screening and early diagnosis

"Personal health management, starting with a falls prevention initiative"—launching validated and operational schemes for early diagnosis and prevention of falls. Falls are the dominant cause of injuries among elderly people. They account for 29% of fatal injuries amongst older people (60+) and this percentage increases sharply after the age of 70. At the same time, they are the most preventable, and their prevention would reduce the need for carer assistance. It, therefore, becomes crucial to overcome limited awareness and usage of innovative solutions to prevent and monitor falls and make these available throughout the EU. Cooperation is needed across traditional system and professional boundaries to foster innovative organization, delivery and business models, supported by high performance and effective information and communication technology (ICT) tools.

Example

A private–public action for the implementation of a fall prevention initiative combining innovative tools for screening (e.g., sarcopenia), monitoring, exercising, and maintaining balance functionality.

"Action for prevention of functional decline and frailty"—launching an initiative for preventing functional decline (with first action focused on physical frailty and malnutrition) among elderly people supported by tools, networks and information. Given the high prevalence of frailty among older people, support of preventive actions offers an opportunity for significant improvement in functional status and quality of life of older people, even with very low cost interventions. A consensus on a clinically validated frailty model, as well as operational definitions will advance the development of targeted interventions (including clinical

trials), products and services aligned with clinical goals. This can be facilitated using innovative tools to support new types of services.

Example

Use of an already developed early diagnostic tool-set (e.g., Functional Capacity Evaluation tool) including innovative medical devices to identify pre-frailty conditions.

The Pharmaceutical Industry's vision is fully consistent with the strategy of the Active and Healthy Ageing European Innovation Partnership (AHA-EIP) launched in March 2012 by the European Commission [18], and a comprehensive project for the integrated treatment of physical frailty and sarcopenia (PF&S) [19], was proposed in 2013 by the pharmaceutical industry with the overarching objective of answering to an unmet medical need deserving integrated scientific and regulatory appraisal.

Industry point of view on PF&S

Over the last two decades, several geriatric conditions have emerged, like osteoporosis, cognitive impairment, and more recently sarcopenia, which triggered investments for innovative development of treatments for specific geriatric indications. Common features of these emerging and increasingly prevalent conditions are direct correlation with aging, gradual manifestation, and function as a risk factor in patients with concomitant diseases and medications. These syndromes lead to loss of physical and/or mental functions and to harmful complications, like fractures, cognitive or mobility disability, decreased healthy life expectancy, all of them very negatively affecting healthcare expenses.

Today sarcopenia is increasingly being recognized as the biological substrate underlying the development of physical frailty, and a key mechanism leading to the negative outcomes of frailty. In practice, mobility disability and physical dependency represent a common cause of nursing home admission. Since sarcopenia emerged in 1988 as a defined clinical entity, its initial definition of decreasing lean body mass with age has been revised and it now encompasses associated decrease in muscle strength and function [20–22] and is a major cause of the broader physical frailty syndrome [22].According to the Foundation for the National Institutes of Health (FNIH) sarcopenia criteria, incorporating both low lean mass and poor function, the prevalence of sarcopenia in community-dwelling older persons is relatively low—between 0.5 and 5.3% in men and 1.8 and 13.3% in women compared with previous definitions based on muscle mass alone [23]. The new criteria also allow appraisal of sarcopenic obesity; nevertheless they need to be tested in more subpopulations and in particular in older persons with higher burden of comorbidities or functional limitation [21]. In a subgroup of the original sample, they are associated with increased risk of incident mobility impairment [24]. Prospective longitudinal studies have demonstrated that older people with sarcopenia are at increased risk of falls and mortality [25, 26].

The direct health care cost attributed to sarcopenia in 2000 was estimated at $18.5 billion ($10.8 billion in men, and $7.7 billion in women) and could be as low as $11.8 billion and as high as $26.2 billion.The excess health care expenditures were $860 for sarcopenic men and $933 for sarcopenic women. A 10% reduction in the prevalence of sarcopenia would result in savings of $1.1 billion per year [27]. Although this study is currently unique and, until now, no reliable economic assessment of sarcopenia has been performed in Europe, it is evident that sarcopenia contributes to several components of public health at both the patient and the societal levels. It interferes with the incidence and prognosis of many comorbidities, and increases health care utilization. It is a determinant of loss of independence, leading to institutionalizations or prolonged hospitalizations. All these aspects increase healthcare costs for the society [28].

Currently, the main stay of intervention for sarcopenia includes prescribed physical activity [22] with proper nutrition [29, 30]. However, as for all chronic disorders, strict adherence to regular physical activity and nutrition plans is difficult to maintain over time.

Today innovative candidate products are being developed, targeting various mechanisms involved in the loss of muscle mass and function. However, before these compounds can be evaluated and approved, clear regulatory recommendations should be provided concerning the adequate methodology for clinical trials, particularly concerning the characterization on the patient population (the clinical profile and the degree of functional loss), as well as the main efficacy endpoints and their expected level of improvement. The use of biomarkers as surrogate endpoints is a further element to be clarified in collaboration with regulatory experts.

1. What types of patients should be selected in clinical trials for sarcopenia?
2. How large should the target population be, and based on this, how large should clinical trials be to adequately assess safety?
3. What endpoints are clinically meaningful?
4. If surrogate endpoints are contemplated, which ones best predict clinically meaningful outcomes?
5. How many primary and secondary endpoints need to be measured to provide adequate information for assessment of efficacy and safety?

Of note, these questions are not specific to sarcopenia, but constitute a generic approach valid for any geriatric condition for which a pharmaceutical intervention is developed.

A role exists for the pharmaceutical industry to develop and invest in specific geriatric indications, and their supportive methodologies. To be effective in health economics terms these projects should evolve mostly in the form of treatment of early detected, still uncomplicated geriatric conditions.

In 2013, the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Commission initiated and funded a large ad hoc precompetitive clinical research project in the field of PF&S as prototypal geriatric indication in the framework of the Innovative Medicines Initiatives (IMI), a joint undertaking between the European Union and EFPIA.

The overall objective of IMI is to improve the drug development process by supporting a more efficient discovery and development of better and safer medicines for patients. IMI supports research projects in the areas of safety and efficacy, knowledge management and education and training. Projects are selected through open calls for proposals.

The project on PF&S was designed to initiate and efficiently conduct a constructive platform discussion of methods in geriatric clinical development, with the contribution of Academia, Regulatory Authorities, Patient Advocacies and other stakeholders. The program was intended to collaboratively review available clinical and epidemiological evidence and agree on operational definitions to fill identified operational gaps. The IMI call on PF&S was published in July 2013 [19], with the overarching objective of answering to an unmet medical need via an integrated scientific and regulatory appraisal.

As discussed in the previous section, frailty can be exemplified as a geriatric physiopathological condition of decreased homeostatic reserve resulting from cumulative declines across multiple physiologic systems. Sarcopenia is a key component of frailty. PF&S constitutes a major risk factor for mobility disability, falls, hospitalization and death. In these terms, PF&S in older people certainly represents an unmet medical need and deserves a more comprehensive clinical appraisal and a regulatory status.

After reviewing the current regulatory frame in the EU, we have identified key actions and deliverables to foster innovative clinical development in specific geriatric indications like PF&S, implying that we will use PF&S as a template for further specific geriatric therapeutic integrated solutions. Integrated solution means a multi-domain combination approach that may or may not include pharmacological agents, and the use of ICT tools for patient monitoring. In fact, geriatric medicine very often requires multifaceted integrated disease management, and it is worthwhile to standardize, rationalize and disseminate it through the implementation of adapted clinical trial methodologies [31].

The IMI PF&S project call encompasses several platforms of regulatory discussion and a randomized clinical trial. Key deliverables can be summarized in five major work-streams:

(1) Development of an operational definition of at-risk subpopulations with undisputable therapeutic need and related therapeutic indication;

(2) Implementation of innovative clinical development methodologies for testing integrated interventions for the prevention of physical frailty and mobility disability;

(3) Qualification of biomarkers of muscle anabolism and catabolism in the physically frail older subject and their correlation with major outcomes;

(4) Achievement of scientific and regulatory consensus on the following elements: therapeutic indication, muscle biomarkers and development clinical methodology;

(5) Developing a health economic model of PF&S in a real life setting.

Essential to the project completion will be the generation and analysis of longitudinal data in a predefined at-risk population though a perspective randomized clinical trial comparing state-of-the-art multi-domain interventions against PF&S.

Interestingly, the IMI PF&S randomized clinical trial will not test any investigational drug, but instead will use structured physical activity, nutrition and ICT in participants randomized to the active treatment arm, and health education and standard of care to those assigned to the control arm. Measuring the efficacy of such a multi-modal intervention in frail older individuals will contribute to establish a reference experimental setting and a package of adapted and agreed methodologies for further integrated pharmacologic development of novel products in this and in similar geriatric conditions [31].

This project is currently ongoing, since July 2014, implemented by the "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) Consortium, which was selected among other projects by an independent experts' panel. The program implementation will last 5 years and includes among others, a clinical work-package to conduct a large multinational randomized clinical trial, a regulatory work-package for the upfront validation of the trial methodology, and an ICT work-package for the integrated use of data of different source: electronic CRF (clinical data and standard biological tests), physical activity recording through an ad hoc device, body composition, and research biomarkers within a web-based data warehouse. See also http://www.mysprintt.eu/.

Overall, we consider the objective elements that define PF&S as a specific unmet medical need of a specific subpopulation of older persons. PF&S also deserves effective and safe treatments targeted on its pathogenetic mechanisms, namely sarcopenia. Modern pharmaceutical industry needs to operate within consistent regulatory and public health policy frames. These should acknowledge specific geriatric conditions, responding to older patient's unmet needs by providing regulatory guidance, plus promote and adequately streamline well adapted, innovative clinical trial methodologies.

The SPRINTT program is progressing in that way by integrating early scientific advice by the EMA as a well identified project deliverable.

Conclusions

The evolution in regulatory thinking on the collection and relevance of clinical data in older patients for clinical development is a milestone in recognizing the emergent importance of aging and geriatrics in public health.

From the point of view of industry, the emphasis is over the recognition of specific conditions related to the older age. Geriatric conditions like PF&S may deserve adapted clinical development, both in terms of adapted methodology when implementing clinical trials and even further in defining the correct methodology for the new indications.

Consistently with the European Commission AHA-EIP, we focus on the public health interest to develop novel drugs indicated for the prevention and treatment of PF&S to delay mobility disability and extend active and healthy life years.

The SPRINTT collaborative project under IMI is paving the way for adapted methodologies to study PF&S in at-risk older persons and to characterize the population to be treated.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study informed consent is not required.

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