Deterioration of Limb Muscle Function During Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Raolat M Abdulai[1,2]*, Tina Jellesmark Jensen[2], Naimish R Patel[2, 3], Michael I Polkey[4], Paul Jansson[2], Bartolomé R Celli[1, 5], Stephen I Rennard[6,7]

1 Brigham and Women's Hospital, Pulmonary and Critical Care Medicine, 75 Francis Street, Boston, MA
2 AstraZeneca, Respiratory, Inflammation & Autoimmunity, Innovative Medicines and Early Development Biotech Unit, Boston, MA, Gothenburg, SE
3 Beth Israel Deaconess Hospital, Boston, MA
4 NIHR Respiratory Biomedical Research Unit at the Royal Brompton Hospital and Imperial College, London, UK
5 Harvard Medical School, Boston, MA
6 University of Nebraska Medical Center, Pulmonary and Critical Care Medicine, Omaha, NE
7 AstraZeneca, Clinical Discovery Unit, Early Development Biotech Unit, Cambridge, UK, Gothenburg, SE

*Correspondence: rabdulai@bwh.harvard.edu

Abstract

Important features of both stable and acute exacerbation of COPD are skeletal muscle weakness and wasting. Limb muscle dysfunction during an exacerbation has been linked to various adverse outcomes, including prolonged hospitalization, readmission, and mortality. The contributing factors leading to muscle dysfunction are similar to those seen in stable COPD: disuse, nutrition/energy balance, hypercapnia, hypoxemia, electrolyte derangements, inflammation, and drugs (i.e., glucocorticoids). These factors may be the trigger for a downstream cascade of local inflammatory changes, pathway process alterations, and structural degradation. Ultimately, the clinical effects can be wide ranging and include reduced limb muscle strength. Current therapies, such as pulmonary/physical rehabilitation have limited impact due to low participation rates. Recently, novel drugs have been developed in similar disorders and learnings from these studies can be used as a foundation to facilitate discovery in patients hospitalized with a COPD exacerbation. Nevertheless, investigators should approach this patient population with knowledge of the limitations of each intervention. In this concise clinical review, we provide an overview of acute muscle dysfunction in patients hospitalized with acute exacerbation of COPD (AECOPD) and a strategic approach to drug development in this setting.

Introduction

Skeletal muscle weakness in association with reduced exercise capacity is frequently seen in patients with stable chronic obstructive pulmonary disease (COPD) (1). Sarcopenia is often used to describe this state of abnormally low lean muscle mass combined with reduced muscle strength or function (2). While this condition is considered to be a feature of aging, it has also been used in the specific context of COPD (3). Cachexia, on the other hand, is a more dynamic disorder in which active fat-free mass loss occurs in association with progressive pathologic processes such as cancer and COPD (4). Whether due to sarcopenia or cachexia, skeletal muscle weakness is more prevalent and severe in COPD than in age matched seniors (1, 4) and is worsened by acute exacerbations of the disease (5). Although clinical consequences of muscle dysfunction in the setting of an acute exacerbation of COPD (AECOPD) is incompletely understood, observations in recent studies have highlighted the importance of the relationship between muscle dysfunction and outcomes after hospitalization for AECOPD. For example, the likelihood of a first or subsequent hospital admission for a COPD exacerbation is correlated with reduced quadriceps bulk at time of discharge (6) and poor exercise performance (7, 8). Conversely, anabolic stimuli in the form of formal post-discharge pulmonary rehabilitation (PR), reduces both readmission and ER visits (9, 10). Despite these findings, the degree to which exacerbations may impact muscle function is variable and likely related to the underlying chronic dysfunction and the severity of illness occurring with the exacerbation, amongst other factors. Thus, the aim of this review is to focus on contributing factors to limb muscle weakness, current and emerging therapies for acute muscle dysfunction, and to outline clinical trial concepts for drug development in this area.

Chronic Muscle Dysfunction in Stable COPD

Limb muscle dysfunction in COPD negatively affects quality of life (QoL), morbidity, and mortality (4). It is characterized by reduced muscle strength and/or endurance (4, 11), with the

lower limbs generally being more affected than the upper limbs (12, 13). Reduced skeletal muscle mass, using fat-free mass index (FFMI) as a surrogate measure, is present in 4-39% of COPD patients (14, 15). While the prevalence generally increases with disease severity, reduced FFMI and quadriceps muscle mass have been reported across all GOLD spirometric stages (1, 16) and body mass index (BMI) categories (17).

Several cellular signaling pathways that may contribute to the imbalance between muscle protein synthesis and protein breakdown have been implicated in limb muscle mass loss in COPD patients (Figure 1). These pathways, together with other initiating factors, may lead to the changes observed in the peripheral muscles of this population (Figure 2).

The morphological and biochemical changes in the peripheral muscle may in part be consequences of physical inactivity and can to some extent be reversed by training (18). Indeed, reduced quadriceps volume, capillarity, and strength is already present in mild COPD and is associated with reduced physical activity (16, 19). The chronic use of tobacco may be another contributor to skeletal muscle dysfunction, as smokers without obstructive lung disease have lower weight and lean body mass (LBM) compared to never smokers (20). Moreover, smokers or former smokers have weaker quadriceps than never smokers and annual loss of fat-free mass is faster in COPD patients who continue to smoke (1, 20).

Acute Dysfunction in Exacerbations of COPD

While the research on muscle dysfunction in the chronic setting may provide a guide for assessing acute muscle dysfunction, the evidence surrounding the latter is limited. Muscle dysfunction in AECOPD may also have parallels with intensive-care acquired weakness (ICUAW), particularly in the area of protein homeostasis (21). Although, it should be noted that there are important differences as follows; first, COPD patients always (whether diagnosed or not) have antecedent morbidity. Second, while certain associated characteristics such as inflammation or immobility are present in both conditions, ICU patients experience an extreme

variety of these features. Although clearly more research is required to further elucidate the mechanisms which occur in the context of AECOPD, this monograph will review some prominent factors which are believed to contribute to muscle dysfunction in this patient population (Figure 2).

Disuse Atrophy

Muscle disuse causes dysfunction through reduced protein synthesis and increased protein catabolism (22, 23), processes characteristic of inactivity. During hospitalization for AECOPD, which can last a median of 7 days (24), most patients spend less than 10 minutes per day walking (25). Of note, it has also been recently demonstrated that exacerbations treated as an outpatient are also associated with reduced physical activity (26). The specific effects of reduced activity in patients hospitalized for AECOPD can be further extrapolated from observations made in studies of normal healthy individuals submitted to bed rest (27). Within one week, reductions in body weight, leg lean mass, and strength were more pronounced in elderly compared to younger individuals (23). In some cases specifically assessing AECOPD, quadriceps muscle force is reduced and quadriceps cross sectional area (Q_{csa}) has been observed to decrease by up to 5% over five days of hospitalization (25, 28). While Greening and colleagues found reduced Q_{csa} in hospitalized AECOPD patients was linked to rehospitalization, longer hospital stays, and increased mortality (6), the same could not be said for the quadriceps maximal voluntary contraction (QMVC). They found that QMVC was not associated with rehospitalization or death after one year. Upper body strength, as measured by handgrip strength (HGS), has been found to be reduced in hospitalized exacerbating COPD patients (28). The HGS test has also been associated with increased mortality for COPD patients with values below the 10^{th} centile (29). However, this parameter may be non-specific as it is often diminished in the elderly and those with chronic diseases (29, 30). Irrespective of their hospitalization status, COPD patients who exacerbate have deterioration of the BMI,

obstruction, dyspnea and exercise capacity (BODE) index score, which does not return to baseline even after one year (31). There are numerous other physiological and functional consequences of an exacerbation, however, studies on the best tools to measure these changes in such a setting are lacking. We have summarized methods for the measurement of muscle dysfunction in COPD with particular focus on those applicable to AECOPD (Table 1) (4, 32).

Energy Imbalance

Weight loss has been observed in hospitalized AECOPD patients (33) and may be due to reduced protein synthesis as seen in ICUAW (21). Additionally, weight loss can worsen during hospitalization for those who are already underweight COPD patients (34, 35). In stable COPD, a negative balance between energy intake and expenditure has been attributed to increased work of breathing (36, 37). This is further aggravated during a severe exacerbation when the resting energy expenditures (REE) rises partly in response to increased oxygen cost of ventilation, consequently leading to negative changes in body weight and muscle mass (37, 38). The growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis positively affects protein synthesis in both the acute and chronic settings (35, 39). In the early phase of an exacerbation, IGF-1 may be elevated in response to hypoxemia or as a stress response and then be reduced in the recovery phase, under the influence of corticosteroids, a suppressor of the GH/IGF-1 axis (35, 39). Additionally, leptin increases during the first days of an exacerbation, while patients are in a low intake/high REE state. Even though leptin should decline as REE decreases and food energy intake increases, in some patients it can remain elevated after 15 days (38, 39). The mechanism for this elevation is thought to be secondary to glucocorticoid use and systemic inflammation (39).

Local and Systemic Inflammation

In reality, leptin is one of many proteins that are altered in response to systemic inflammation during AECOPD (38). In fact, there are alterations of multiple systemic cytokines (TNF-α), acute phase reactants (CRP), and other proinflammatory markers including fibrinogen (38, 40, 41). However, there is limited information regarding the character of the local inflammatory response at the muscle level (28, 42). Crul and colleagues found similar levels of IL-6 and IL-8 mRNA expression in the vastus lateralis muscle in those hospitalized for AECOPD, stable COPD patients, and healthy adults (42). However, the AECOPD patient biopsies were performed on hospital day 4 and may have been influenced by glucocorticoids. On the other hand, Spruit et al. found that local IL-6 and IL-8 levels were inversely proportional to isometric quadriceps strength. Additionally, increased circulating IL-8 levels were independently associated with the variance observed in handgrip and quadriceps strength in hospitalized AECOPD patients (28). Given the inconsistent findings, additional studies are needed to evaluate the local effect of inflammatory processes on muscle function and repair during an exacerbation.

Hypoxia and Hypercapnic Acidosis

Hypoxia has an inhibitory effect on muscle protein synthesis by activating muscle proteolysis via stimulation of calcium-dependent proteases, while acidosis stimulates proteolysis mainly via the ubiquitin-proteasome pathway (43). Due to inhibited hydroxylation, hypoxia inducible factor-1α (HIF-1α) is elevated in skeletal muscle during hypoxic states (44). The elevation of HIF-1α causes a downstream cascade of alterations in glucose and oxidative metabolism, and DNA alteration affecting myosin heavy chain expression (44). The molecular mechanism for these local changes may be due to reduction of intracellular muscle pH, resulting in changes in myoelectrical signaling and reduction in muscle fiber conduction velocity (45, 46). Utilizing NMR spectroscopy, it has been demonstrated that some stable COPD patients develop a marked

quadriceps acidosis during a sustained contraction (47), which is not seen in the upper limb suggesting a mechanistic role for changes to muscle morphology. Even though the COPD patients were sicker than the controls in this study, the results suggest potential interaction between hypercapnia, acidosis, and exercise-related fatigue (sustained contraction) which warrants further examination.

Electrolyte Dysfunction

Electrolyte imbalance, particularly hypokalaemia and hypophosphatemia are recognised causes of muscle dysfunction. Intuitively one might think these disorders likely in patients who, in addition to aggressive treatment with beta-agonist, often require diuretic therapy for co-morbidities and which may be worsened by the presence of hypercarbia (48). Few data exist in AECOPD, but it is clear that both hyponatremia and hypokalemia can occur (49, 50), although their impact on muscle force in this context is unknown. Older studies of COPD patients with respiratory failure (in comparison with controls), found reduced intramuscular potassium, phosphorus, and magnesium but increased intramuscular chloride, sodium, and water (50, 51). However, correlation with muscle function tests were not performed, leaving an opportunity for newer studies to evaluate the role of electrolyte abnormalities in muscle dysfunction of AECOPD.

Glucocorticoids

Glucocorticoids, frequently used during AECOPD (52), indirectly reduce protein synthesis through downregulation of IGF-I (53, 54). In addition, glucocorticoids have been implicated in the elevation of leptin seen in the early days of an exacerbation (38) and activation of skeletal muscle mitochondrial-mediated apoptotic signaling pathways (55). Although glucocorticoids contribute to a negative nitrogen balance in both acute exacerbations and stable disease (56),

corticosteroid use has not directly been linked to a reduction in muscle mass in stable patients (57) nor a change in quadriceps strength (58). Furthermore, the correlation between glucocorticoid dose and quadriceps strength is not straightforward (28) thus, raising the hypothesis that the effects may be an interaction between the steroids, immobility, and/or inflammation and not simply a steroid effect alone.

Therapies for Muscle Dysfunction in the AECOPD Population

The currently available therapies for muscle dysfunction in AECOPD include pulmonary rehabilitation (PR), neuromuscular electrical stimulation (NMES), and nutritional support (Table 2a).

Pulmonary Rehabilitation and Specific Muscle Training

Exercise training for AECOPD patients can be generalized or limb (upper or lower) specific with the goal of improving performance, endurance, and strength (4, 59-61). Ultimately, the objective of this aspect of pulmonary rehabilitation (PR) in AECOPD may be two-fold: to prevent loss and/or induce recovery. A Cochrane review of nine studies in AECOPD patients found benefits in readmission and mortality in those undergoing inpatient and/or outpatient PR soon after an exacerbation when compared with usual care (60). However, two recent studies in AECOPD and ICU patients suggests the benefits may be limited (62, 63). Greening and colleagues initiated PR during hospitalization and showed fewer benefits and potential concerns for early (inpatient) PR initiation when used in conjunction with NMES (62). Further, they found no difference in QMVC of those who were not readmitted regardless of study group assignment (62). Notably, there was limited exercise training during hospitalization (average of <3 sessions each of aerobic and resistance training) and limited use of PR following hospital discharge in the intervention group. Additionally, a randomized trial of standard rehabilitation versus usual care in 300 patients admitted to the intensive care unit because of respiratory failure did not yield any

advantage in patient-related outcomes (63). While the reason for these results are unclear, it may be prudent to initiate PR once the patient's full capacity to participate in rehabilitation returns to a level tolerable of increasing workloads. Despite these controversies, informed opinion suggests that PR is severely underutilized for multiple reasons including patient perception of benefit and feasibility of travel (61). Regardless of the goals or methods of PR in the acute condition, the stability and individual needs of the patient should be considered before initiation.

Neuromuscular Electrical Stimulation

NMES is the application of electrical current over target muscles stimulating motor neurons and causing a muscular contraction (4). Zanotti et al. showed that muscle strength improved with active limb exercises and electrical stimulation in mechanically ventilated COPD patients (64). The largest study in this area is that of Greening and co-workers who assessed 386 subjects, of which 82% (n=320) were patients admitted with a COPD exacerbation, to either inpatient rehabilitation using a regime incorporating NMES *vide infra* or best supportive care (62). As discussed above, this study failed to demonstrate a benefit for inpatient rehabilitation and revealed higher mortality in the intervention group which might have been due to reduced uptake of rehabilitation post-hospitalization (62). Therefore one concern for NMES may be the timing of application, given the anabolic/catabolic balance shifts throughout AECOPD (65). Recently, NMES has shown to be useful in stable COPD outpatients (66) and may yet have a role during early convalescence from AECOPD. More studies are needed, to define the population that could benefit from this therapy.

Nutritional Support and Supplements

Reduced intake of nutrients such as proteins and fats in the first few days of hospitalization has led to suggestion for a high protein diet (37). In fact, a dietary protein intake of >1.5 g/kg/d has

been suggested as a means to prevent weight loss following an exacerbation based on studies in this population (4, 37). More generally, a recent retrospective study showed that patients with a primary diagnosis of COPD who received complete oral nutritional support (ONS) while hospitalized, experienced a reduction in length of stay by 1.9 days and a 13.1% lower chance of 30-day readmission (33). As this study was performed using Medicare claims data, the nutrition programs of the hospitals analyzed may vary, limiting the recommendations that can be distilled from the study results. Indeed, Puthucheary and colleagues found that administration of protein for ICUAW was associated with increased muscle wasting (21). However, this study may be of limited applicability to the AECOPD setting, as only a small number of COPD patients were included (9 out of 63, 14.3%), a third of all subjects had no antecedent chronic illness, and many experienced multi-organ failure during their ICU course. In addition to ONS and bulk protein administration, nutrients such as creatine and co-enzyme Q10 have been evaluated as potential therapies to treat muscle dysfunction in COPD but have been met with poor or limited results (67, 68). Finally, while vitamin D appears to be important for skeletal muscle health as demonstrated by studies in both murine and human models (69, 70), its importance in acute muscle dysfunction in COPD has not been fully evaluated. Due to the mixed data, surrounding nutritional and protein administration for acute muscle dysfunction, nutritional risk screening and phenotyping with biological markers have been suggested prior to instituting a specific regimen (36).

Emerging Therapies

The major classes of emerging therapeutics for muscle dysfunction are androgens, myostatin inhibitors, GH analogues, and ghrelin receptor agonists (Table 2b). Several of these drugs directly increase muscle mass and/or function. However, studies of these therapies have been focused mainly in chronic or subacute debilitating diseases such as cancer and heart failure and most lacked the inclusion of structured exercise and nutritional plans.

Androgens and Progesterone

Anabolic steroids affect muscle tissue by inducing protein anabolism via androgen receptors while inhibiting catabolism through neutralization of the glucocorticoid receptor (71). Unlike bulk protein administration during acute illness, androgens do not generate large quantities of urea and heat (71). Nandrolone and oxandrolone have been the best studied androgens in COPD (72, 73). Oxandrolone was approved for patients with weight loss due to chronic infection, extensive surgery or idiopathic failure to thrive (73). Oxandrolone increased LBM in an open-label, prospective, multicenter trial of a stable outpatient COPD population with cachexia. However, the applicability of the results of the study are limited due to the lack of a control group and high dropout rate (73). Testosterone has been reported to be low in some COPD patients, although an association with reduced muscle function has not consistently been shown (72, 73). However, in a 4-way study with resistance training in COPD (74), participants who were randomized to receive both training and testosterone gained the most muscle mass. Concerns regarding testosterone's side effects have limited its use but this may be mitigated by using selective androgen receptor modulators (SARM). SARMs, studied in cancer cachexia, have shown potential to increase weight, strength, and function (75, 76) while minimizing the side effects often seen with testosterone treatment. Finally, megestrol acetate may benefit muscle dysfunction due to its effect on appetite and weight gain, in addition to stimulating ventilation. In one study, the drug increased weight in COPD patients but, like several other androgens, failed to significantly improve 6-MWD (77).

Myostatin Inhibitors

Myostatin, a member of the transforming growth factor-β protein superfamily, is a negative regulator of muscle growth and is elevated in states of cachexia including COPD (78). There are several drugs in this category, including bimagrumab (BYM338), landogrozumab (LY2495655),

AMG/PINTA 745, and trevogrumab (REGN-1033) (Table 2b). Bimagrumab (BYM338) which blocks the type IIb Activin receptor, has been studied in various diseases states including stable COPD, sarcopenia, and inclusion body myositis (79, 80). In the COPD study, bimagrumab showed statistically significant increase of up to 7% in thigh muscle volume (TMV) by MRI at 4, 8, and 24 weeks when compared to placebo (80). There was no improvement in functional outcomes including the 6-MWD. In a four-week study of prostate cancer patients receiving androgen deprivation therapy, AMG 745 caused a 1.5% increase in LBM and 1.7% reduction in body fat when compared to placebo at day 29 but failed to show any improvement in functional parameters (81).

Growth Hormone

Once secreted by the anterior pituitary, GH acts via mediators including IGF-1 to initiate a multitude of biological processes. GH regulation of IGF-1 and its interplay with myostatin have been demonstrated in COPD patients (42). Despite its potential uses, there is concern for safety given an important study which demonstrated increased mortality in ICU patients receiving GH (82). The causes of the excess mortality in that study have been debated, but there was a reduction in GH-associated interventional clinical trials in the subsequent years (83). Clinical trials of GH in respiratory patients have yielded mixed results (84, 85). Pape and colleagues performed an uncontrolled study, finding weight gain and increased maximal inspiratory pressures in COPD patients treated with recombinant GH (85). In another study, a randomized controlled trial, COPD patients showed no improvement in strength and endurance compared to placebo and worse 6-MWD (84).

Ghrelin

Due to controversy surrounding the safety of GH, increasing enthusiasm exists for the use of growth hormone secretagogues such as ghrelin and ghrelin receptor agonists. Ghrelin

stimulates secretion of GH, via growth hormone secretagogue receptor 1a (GHS-R1a), leading to regulation of multiple functions from food intake to glucose metabolism (86). In humans, ghrelin has been studied in cancer cachexia, sarcopenia of the elderly, chronic heart failure and COPD (87-91). In COPD patients, ghrelin improved LBM and muscle strength, but had mixed results on functional outcomes such as the 6-MWD (87, 90). SUN11031, another synthetic human ghrelin, was studied by Levinson and Gertner in clinical stable cachexic COPD patients (89). This study enrolled 192 patients with BMI <21 kg/m2 and FFMI <16 kg/m2. Results showed that up to 65% of subjects in both treatment groups gained at least 3% of their body weight after 85 days of treatment (89). Another drug, capromorelin, was tested for 1 year in adults > 65 years old with evidence of functional decline based on the SF-36 Health Survey and HGS (88). After 12-month treatment, there was a 7% increase in stair climb (vs 0.9% placebo, p=0.02) and a decrease in tandem walk time.

Finally, anamorelin has shown promise in cancer cachexia. Results of "Anamorelin in Patients with Non-small-cell Lung Cancer and Cachexia" (ROMANA 1 and ROMANA 2) studies showed an increase in LBM but no improvements in functional outcomes such as handgrip strength (91).

<u>Considerations for Drug Development to Treat Acute Muscle Dysfunction</u>

Given the learnings from therapeutic studies performed in stable/chronic settings and in non-COPD subjects, we have developed recommendations for drug development targeting muscle dysfunction in hospitalized AECOPD. These recommendations are summarized in Table 4, while further considerations may be found in recent review by Steiner and colleagues (92).

Inclusion/Stratification

The studies of emerging therapies in the stable COPD setting have shown inconsistent improvement across parameters of muscle dysfunction (Table 2b). In an acute setting, it is possible that these drugs may provide greater benefit due to the degree and nature of muscle

dysfunction. Therefore, careful consideration needs to be given to the inclusion criteria for a study with a novel intervention. Given current knowledge, it seems sensible to stratify entrance into the study by physical performance, muscle strength, and/or skeletal muscle composition. Based on recent studies, Q_{CSA} may be a useful inclusion criterion due to its predictive ability and bedside accessibility (6, 93). While QMVC was found to be variably impacted in AECOPD and therefore limited as an outcome (62), it may prove to be a good stratification tool in order to direct therapy towards the most affected individuals. Depending on the severity of the exacerbations, assessment of physical capacity using a tool such as the short physical performance battery (SPPB) can inform on weakness in the lower limb (94), and the four-meter gait speed (4MGS) component is predictive of readmission in the context of AECOPD.

Outcome Measures

In conjunction with determining the appropriate inclusion criteria for the study, endpoint measurement(s) must be established. Regulatory endpoints fall into two major categories: objective physiological assessments (pulmonary function tests and exercise capacity) and patient-reported outcome measurements (symptom scores, activity scales, and health-related quality-of-life instruments) (Table 3) (95). The SPPB, which is widely used in gerontology and relates to quadriceps structure and function in COPD (94), has recently been suggested by the European Medicine Agency for use in clinical trials (96). Additionally, sub-maximal constant work rate endurance time is being prepared for submission for qualification (97).

Another endpoint which may in due course be validated as an outcome is the European Union Innovative Medicine Initiative Patient reported outcome (PROactive) tool (98) which aims to capture the patient experience of physical activity. The consortium conducted a 6-week, multicenter, randomized, two-way cross-over study in 236 stable and exacerbated COPD patients. The scores on the questionnaire correlated with patient QoL, dyspnea, and exercise

capacity (98). Finally, endpoints such as hospital 30- or 90-day readmission can be utilized as an objective non-physiological assessment, while having the value of being attractive to payers (e.g., insurance companies) and prognostic indicators of mortality (99, 100).

Timing

The timing of the intervention and duration of administration are important parameters that, while dependent the drug's mode of action, require careful coordination with patient discharge planning. In hospitalized AECOPD, initiating treatment at the time of discharge or shortly after discharge has several advantages. The first advantage is knowing that the patient is to survive hospitalization given the inpatient morality rate of 2-5% (99, 101). Additionally, initiating treatment after discharge allows for confirmation of AECOPD diagnosis and fewer confounding factors, such as use of systemic glucocorticoids.

Duration

Duration of treatment can vary depending on the characteristics of the drug. For example, bimagrumab increased TMV at 8 weeks of treatment (80), though there was no evidence of functional improvement. With due consideration for a medicine's mode of action, a longer treatment period with a minimum of 3 months may provide enough time for assessment of physiological, functional, and non-physiological endpoints. Stable outpatient COPD and mechanically ventilated exacerbated COPD patients may require longer or shorter lengths of treatment depending on the goal of the trial.

Adjunct Therapy

Many of the drug studies we reviewed did not include PR or nutritional interventions. For prevention and intervention studies in sarcopenia the preference is for incorporation of exercise and nutrition because of perceived benefits (102, 103). However, in the recovery phase from

AECOPD, PR and nutritional interventions might obscure benefits from a potentially effective medicine. Thus, in early phase trials designed to provide a 'reason to believe' it may be desirable to include an arm that does not contain formal PR or allow PR based on physician discretion with understanding of the variability it may introduce into the study.

Conclusion

It is now accepted that muscle weakness and consequent limitation to ADL's and exercise is a feature of COPD. During a hospitalization for an exacerbation, muscle strength, physical activity, and exercise performance are further impaired and are markers of increased future risk. Therefore, the period around an exacerbation represents a crucial moment to explore interventions that may reverse these processes. In the chronic setting, there have been mixed results in therapeutics for muscle dysfunction. An improved understanding of the contributing factors to acute muscle dysfunction and important clinical trial concepts for drug development in this area may prove a promising therapeutic avenue to reduce morbidity associated with hospitalization for AECOPD. The recent efforts to improve evaluation of outcomes in this population, including the PROactive consortium, will ensure future availability and adoption of drug development tools that are accepted by regulatory agencies to expedite the development of novel therapies focused on muscle dysfunction in the acutely ill COPD patient.

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