MODIFYING ALPHA-1 ANTITRYPSIN DEFICIENCY-RELATED EMPHYSEMA: FROM EVIDENCE TO PRACTICE

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Chairpersons

Noel Gerard McElvaney,[1] Ilaria Ferrarotti[2]

Speakers

Joanna Chorostowska-Wynimko,[3] Kenneth R. Chapman,[4] A. Rembert Koczulla[5]

1. Professor of Medicine, Head of Department, Royal College of Surgeons, Dublin, Ireland
2. Centre for the Diagnosis of Hereditary Deficiency of α1-antitrypsin, Department of Internal Medicine and Therapeutics, Pneumology Section, University of Pavia, Pavia, Italy
3. Department of Genetics and Clinical Immunology, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
4. Professor of Medicine, Asthma and Airway Centre of the University Health Network, University of Toronto, Toronto, Canada
5. Department of Internal Medicine, Section of Pulmonary Diseases, University of Marburg, Marburg, Germany

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MEETING SUMMARY

The symposium discussed the role of disease modification in alpha-1 antitrypsin deficiency (AATD)-related emphysema. Evidence from the recent RAPID trial and its extension trial showed that treating AATD patients with intravenous alpha-1 antitrypsin (alpha-1 proteinase inhibitor; [A_1-PI]) therapy slowed the rate of lung density decline and had a disease-modifying effect. By modifying the course of disease, survival can be extended by several years. Dr Ferrarotti opened the symposium by introducing the topic of AATD-related emphysema, highlighting the latest epidemiological data, and providing an overview of the treatment landscape. Prof Chorostowska-Wynimko then addressed how to determine the disease modification that occurs in AATD, focussing on the clinical trial design (classical parallel-group, placebo-controlled trial design versus a 'late-start' study design) and clinical outcomes (forced expiratory volume in 1 second [FEV_1] versus computed tomography [CT] lung density). Prof Chapman explained the results and the post hoc analyses of the RAPID trials; a sustained reduction in lung density decline rate that proves to have a

disease-modifying effect. Prof Koczulla closed the symposium by relating current evidence to the real-life management of patients, notably how patients should be monitored and the prospect of home-based care.

Welcome and Introduction

Professor Noel Gerard McElvaney and Doctor Ilaria Ferrarotti

AATD is a genetic disease that increases the risk of developing lung disease; in particular, emphysema. AATD-related emphysema is a rare disease, with an incidence of 1 in 4,000 to 1 in 10,000. In the past, intravenous treatment with A_1-PI could not be shown to be effective using comparatively crude spirometric outcomes. However, the RAPID trial showed the efficacy of A_1-PI treatment in slowing down emphysema progression using the more sensitive and specific outcome measure of lung density.

Determining Disease Modification in A_1-PI Antitrypsin Deficiency: Challenges and Lessons Learned

Professor Joanna Chorostowska-Wynimko

Disease modification is best defined as a sustained change in disease state, which is the result of a given therapeutic intervention and characterised by an improvement in or stabilisation of a disease. This is usually due to a reduction in the rate of disease progression that occurs following a therapeutic intervention and may persist after the intervention is discontinued.[1] Disease-modifying therapy should impact the pathological and pathophysiological mechanisms underlying the disease rather than addressing clinical symptoms of the disease alone.[2]

To differentiate disease-modifying therapy from symptomatic therapy, the therapy must alter the rate of decline to slow down disease progression. Currently, none of the approved pharmacological therapies for chronic obstructive pulmonary disease (COPD) have demonstrated an unequivocal disease-modifying effect. One important reason for this is that multiple pathological mechanisms can lead to COPD and no single therapy targets all mechanisms. The accepted mode of proving therapeutic efficacy is the parallel-group, placebo-controlled trial design, which has limitations in the assessment of chronic, slowly progressing diseases that lack sensitive biomarkers or responsive outcome measures. Recently, it was suggested that the optimal clinical trial design for chronic diseases is the 'late-start' study design; this consists of two phases. The first phase followed the standard design whereby patients are randomised into parallel active treatment or placebo groups and any effect observed in the active group may be related to the symptomatic effects of the therapy. In the second open-label phase, patients either continued on active therapy (the Early-Start group) or were shifted from the placebo to active therapy (Delayed-Start group). In the second phase, the disease-modifying effect was analysed by assessing if the difference between both arms was maintained until the end of the study, following which the therapy may be considered as truly disease-modifying.[1]

Although FEV_1 is the accepted biomarker for COPD, it is not the ideal biomarker to address disease modification for several reasons: FEV_1 does not reflect COPD and emphysema mechanisms, it is an indirect measure; it is variable day-to-day and prone to high intra-subject variability, and has a non-linear decline over time.[3] FEV_1 correlates poorly with other outcomes that are applied to clinical trials (such as dyspnoea, exercise capacity, quality of life, number of exacerbations) and is affected by comorbidities, which is a major concern in patients with COPD.[4]

The biomarker broadly accepted in the scientific literature as a reliable and sensitive biomarker of disease progression and decline in AATD-related emphysema, is CT lung densitometry. It reflects changes in lung structure allowing a reviewer-independent quantification of disease severity and distribution, has higher reproducibility and sensitivity compared with lung-function outcomes, and correlates with other outcomes (e.g. the diffusing capacity of the lungs for carbon monoxide [DL_{CO}], FEV_1, mortality, and quality of life).[5] A recent study by Green et al.[6] directly showed the significant link between lung density decline and survival of patients with AATD and emphysema. In the same study, lung-function outcomes were assessed in relation to lung density: FEV_1 was less sensitive but more specific in predicting CT lung density than using the transfer coefficient for carbon monoxide (KCO) (corrected for lung volume) and DL_{CO}.[6] Taken together these physiological measurements of lung disease have very low negative predictive values for CT density decline.

As the causative process has been identified, AATD-associated emphysema should be a good model to evaluate a possible disease-modifying effect of therapy, represented by the sustained slow down of emphysema progression following therapeutic intervention. One of the largest trials exploring the modifying effect of A_1-PI therapy on patient survival included an observational cohort of more than 1,100 patients.[7] Patients with FEV_1 <50% predicted were stratified according to therapeutic intervention into ever-treated and never-treated groups. The mortality rate was significantly higher in the never-treated group (47%) compared with the ever-treated group (18%), and it was demonstrated that FEV_1 decline was significantly slower in patients with AATD with FEV_1 35–49% predicted (p=0.03). Confounding factors of this study included the observational design, varying length of treatment, the socioeconomic background of patients (different healthcare delivery systems and socioeconomic factors), and the use of an inadequate biomarker (FEV_1).[7]

Two randomised trials, the Danish-Dutch study[8] and the EXACTLE study,[9] used lung density decline as a biomarker. Neither study reached statistical significance but the pooled analysis of the two datasets was statistically significant (p=0.006) and showed that A_1-PI therapy affects the rate of lung density decline in AATD-related emphysema.[10] Unfortunately, both studies were underpowered and it was concluded that a larger number of patients was necessary to demonstrate the modifying effect, which is challenging because AATD is a rare disease. Enrolling more patients would mean increasing the number of trial centres, imposing challenges on the standardisation of measurements, and increasing cost. To prove disease modification in AATD, more patients are required, a longer study duration is needed, and most importantly the trial design must allow for assessments that prove that the treatment effect is maintained and not just symptomatic.

Disease Modification in Alpha-1 Antitrypsin Deficiency: Changing the Course of Disease Progression with Intravenous A_1-PI Therapy

Professor Kenneth R. Chapman

The RAPID trial was designed specifically to be able to demonstrate the effect of A_1-PI therapy on CT lung density: 180 non-smoking patients with A_1-PI <11 µM and FEV_1 35–70% predicted, were randomised to receive intravenous A_1-PI therapy 60 mg/kg or placebo once weekly for 24 months. The study design of the RAPID trials is shown in Figure 1. A differential withdrawal was noted with patients in the placebo group being more likely to withdraw before the end of the study than patients in the treatment group (p=0.04). Of those enrolled, 153 patients completed the first phase of the RAPID trial; 84 in the treatment group and 69 in the placebo group. The RAPID Extension trial followed the patients for an additional 24 months.

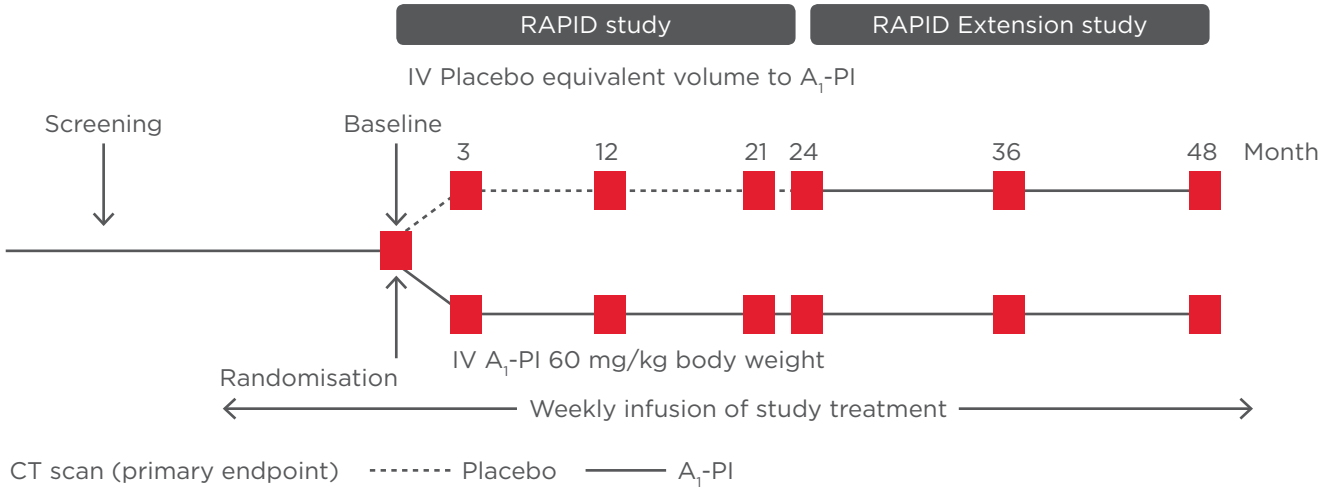

Figure 1: The RAPID and RAPID Extension Trial Study Design.[2]
Primary endpoint: Lung density measured by CT scan at 0, 3, 12, 21, 24, 36, and 48 months.
CT: computed tomography; A_1-PI: alpha-1 proteinase inhibitor; IV: intravenous.

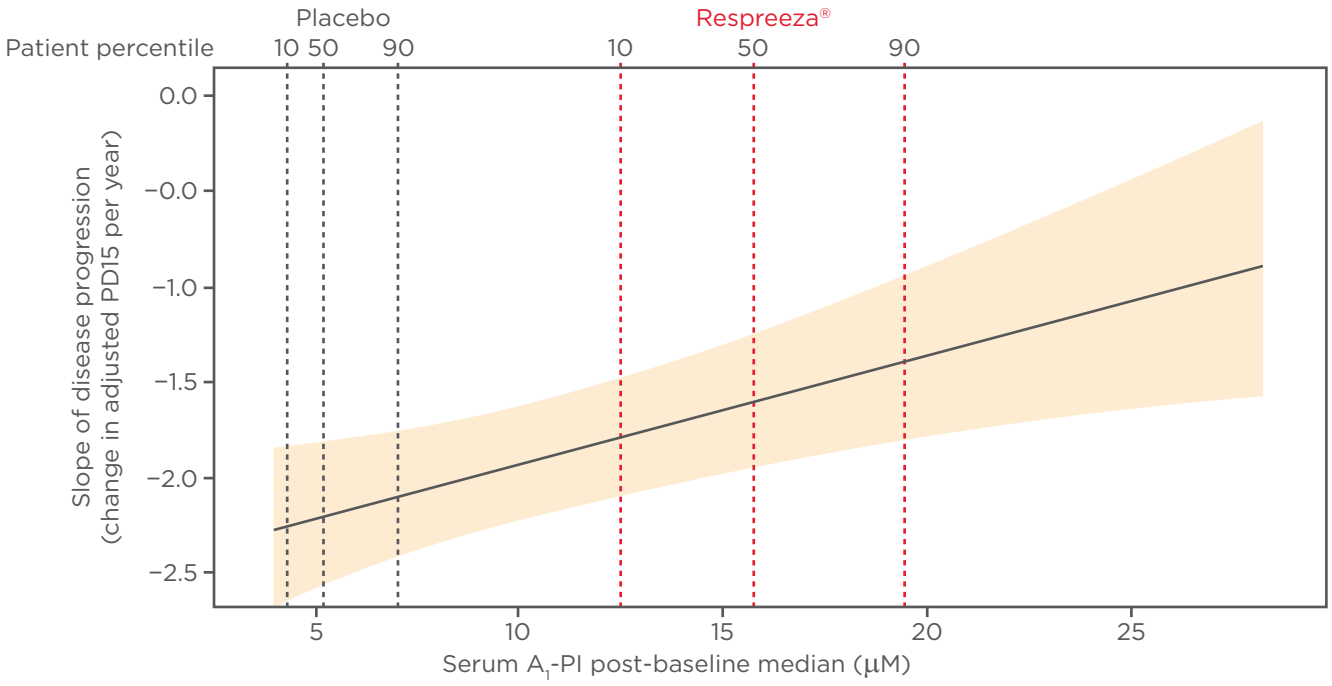

Figure 2: Achieved intravenous alpha-1 antitrypsin levels associated with the rate of change in lung density: RAPID Study.[11]

A_1-PI: alpha-1 proteinase inhibitor; PD15: 15th percentile point.

Patients in the treatment group continued on therapy (Early-Start group) and those in the placebo group were switched to active treatment (Delayed-Start group). All patients who completed the RAPID trial were eligible for the extension trial, except American patients (RAPID Extension trial n=140) (Figure 1). Patient baseline demographics were well balanced for both groups in the RAPID trial: average age was 53.8 years and 52.4 years in the treatment and placebo groups, respectively. Adjusted lung density at the 15th percentile point (PD15) CT was 45.5 g/L and 48.9 g/L for treatment and placebo groups, respectively.[11]

The primary endpoint, loss of lung density, is a surrogate for the loss of lung tissue and was used as the pathological correlate for progression of emphysema. The progression rate of emphysema is determined by a change in lung density measured by a CT scan of the whole lung. The PD15 is extracted from the frequency distribution of lung voxels and is defined by low density units (Hounsfield unit) at which 15% of the voxels in the histogram have a lower density. From prior work, it is known that a shift in PD15 is a way of quantifying loss of lung density.[10,12]

The final outcome was assessed in both groups after 24 months for the randomised placebo-controlled phase and 48 months for the open-label Extension phase of the study.[11] During the RAPID trial, patients in the placebo group had a significantly greater lung density decline compared to those in the A_1-PI treatment group. In the RAPID extension trial, the decline in lung density in the Early-Start group was similar to the first phase, whereas the loss in lung density slowed in the Delayed-Start group. However, lung density lost during placebo treatment was not regained once patients were switched to active treatment.

The results from the RAPID trials allowed the investigators to determine a threshold for a rapid or slow decline in lung density; a decline of >2 g/L per year was considered a fast decline. When the results at 24 months were expressed as a proportion of rapid and slow decliners, 73% and 26% of Early-Start patients were slow and rapid decliners, respectively. Delayed-Start patients (i.e. on placebo) had more or less equal stratification between slow and rapid decline, with 48% slow decline and 49% rapid decline. In the extension phase, the proportion of slow to rapid decliners in the Early-Start group was maintained but in the Delayed-Start group an improvement to 75% slow decliners and 25% rapid decliners was observed.[13]

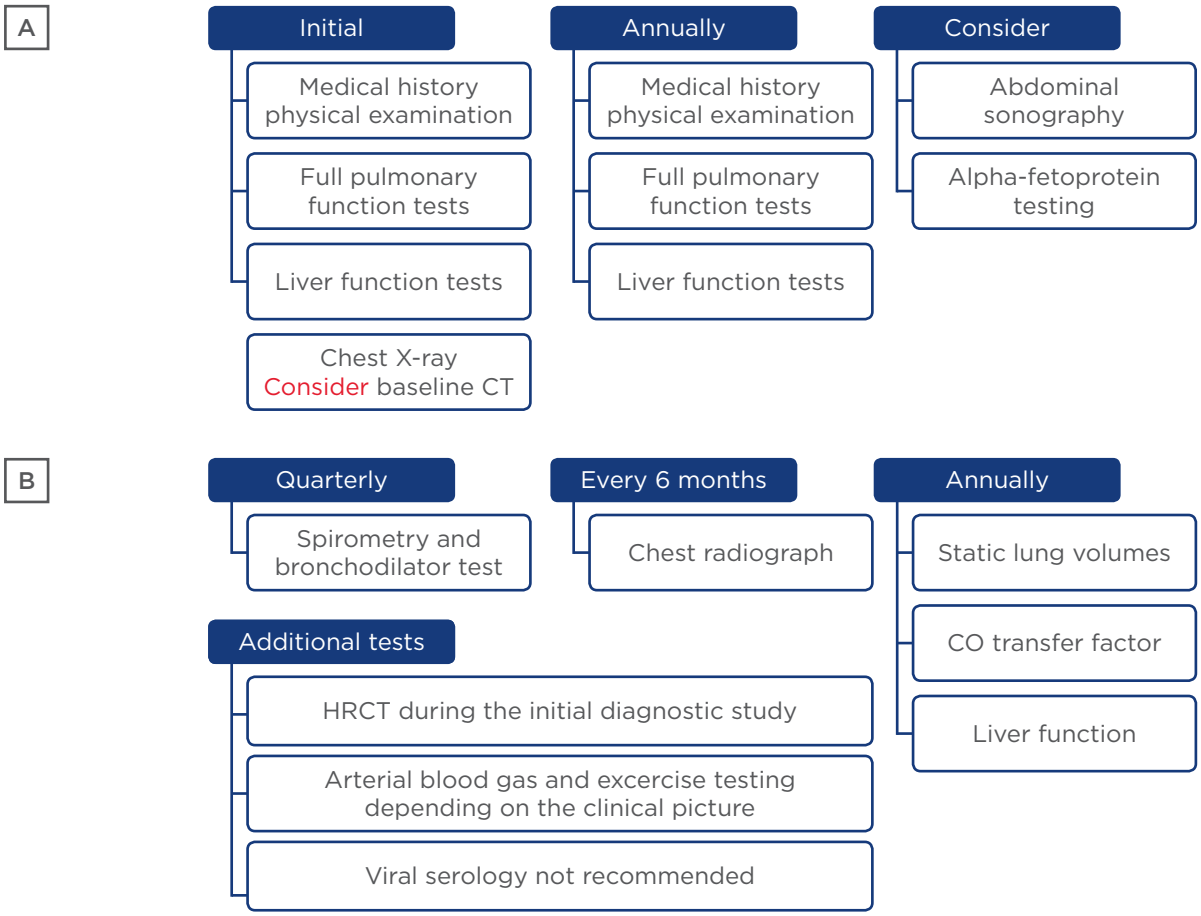

Figure 3: Clinical practice guidelines for monitoring alpha-1 antitrypsin deficiency.

A) Recommendations from the New England Journal of Medicine;[20] B) recommendations from the Spanish Guidelines.[18]

CT: computed tomography; CO: carbon monoxide; HRCT: high-resolution computed tomography.

Factors resulting in a range of serum levels achieved after the infusion of 60 mg/kg include differences in volumes of distribution between men and women, and obese and lean patients. A linear relationship between the plasma levels and the change of adjusted PD15 was observed, suggesting a dose-response to A_1-PI therapy and that higher doses may have a greater effect on slowing disease progression (Figure 2).[11]

In previous studies it was shown that desmosine and isodesmosine (biomarkers of elastin degradation) are higher in the plasma and sputum of patients with AATD compared with patients with non-AATD-related COPD.[14,15] In the RAPID trial desmosine/isodesmosine concentrations were significantly correlated with a loss of lung density, as measured by CT scan.[16] Moreover, after 4 years the traditional but insensitive pulmonary function markers of obstructive lung disease (FEV_1 and forced vital capacity) correlated with the more sensitive marker of CT lung density.[17] By the end of the RAPID trial six patients had died or undergone lung transplantation. The average lung density when these terminal events occurred was 20 g/L, while the average lung density at the start of the trial was 46 g/L. In the RAPID trial placebo-treated patients had a lung density loss of 2.2 g/L/year and active-treated patients had a loss of 1.5 g/L/year, differences that would mean a 6-year life extension in Early-Start patients.[11]

Caring for Patients with Alpha-1 Antitrypsin Deficiency: What Guidelines Do Not Tell You

Professor A. Rembert Koczulla

Monitoring Patients Receiving Intravenous A_1-PI Therapy in Real Life

Currently there is no clear consensus on how often to monitor patients with AATD. Imaging is

crucial to measure baseline severity of disease, rule out other diseases, and guide therapeutic options. However, guidelines[18,19] vary in their recommendations and therefore clinical presentation should guide diagnostics. Silverman and Sandhaus[20] recommend that during the initial assessment, patients with AATD should have a medical history taken, a full physical examination, full pulmonary function testing, liver function testing, and a chest X-ray; baseline CT should also be considered. Annual follow-up abdominal sonography and alpha-fetoprotein testing should be considered in addition to routine tests (Figure 3a).[20] The Spanish guidelines[18] differ slightly, recommending quarterly spirometry including bronchodilator testing, chest radiography every 6 months, and annual static lung volumes, carbon monoxide transfer factor, and liver function testing (Figure 3b). Liver function testing is recommended annually by Silverman and Sandhaus[20] and the Alpha-1 Foundation. Elastography based on sonography[21] and magnetic resonance elastography are non-invasive tests that are currently being explored and may help identify patients with AATD liver disease in the future. Patients with concomitant COPD should be followed up with CT scans or assessed using the modified Medical Research Council (MRC) scale 4–6 weeks after an exacerbation and discharge from hospital.[19]

The Practical Side of Intravenous A_1-PI Therapy

A_1-PI therapy is recommended by the American Thoracic Society/European Respiratory Society (ATS/ERS) for patients with severe AATD and 30–65% FEV_1 predicted, although newer guidelines recommend therapy for a broader range of disease severities.[22,23] In the European Union (EU), three approved products and differences in infusion time exist, although in Prof Koczulla's experience this is not an issue for patients. Differences in drugs have been demonstrated; Zemaira®/Respreeza® contains 1% impurities, mainly albumin, whereas Prolastin® contains 38% impurities.[24] With the differences in purity and application time between the marketed products, one product may meet specific patient needs better than the other.

Patient Issues: What Can I Offer?

Patients that are on a weekly intravenous therapy regimen often ask for guidance on how to continue treatment when they go on holiday. One option would be to infuse a double dose to cover a 2-week treatment period. In the RAPID trial, bi-weekly infusion of 120 mg/kg demonstrated a favourable safety profile with no overall increase in the incidence or severity of adverse events for 120 mg/kg and 60 mg/kg doses of A_1-PI, versus corresponding doses of placebo.[25] The Spanish guidelines recommend up to 180 mg/kg doses accommodating 3-weekly dosing.[18] It should be considered that if an increased dose is administered, a higher volume and a larger amount of sodium will also be administered which will need to be taken into account with coexisting diseases.

In Ireland and France, home-based care is established for patients with AATD. A German study[26] of seven patients and >1,000 infusions (administered by visiting nurses) over 3 years observed no hospitalisations, no allergic reactions, and no severe adverse events. During the weekly visits nurses assessed general health and measured pulse, blood pressure, and oxygen saturation. Additional assessments included a monthly exacerbation-history questionnaire and quarterly spirometry measurements with blood gas analysis. It was concluded that A_1-PI therapy at home was feasible and safe, and achieved consistently high quality-of-life scores.[26]

Non-Pharmacological Treatment

Non-pharmacological therapy is supported by The Global Initiative for Chronic Obstructive Lung Disease (GOLD), where 10–45 minutes of daily to weekly exercise is recommended for patients with chronic disease.[19] A statement by Spruit and the ATS/ERS recommends that patients with chronic disease should exercise with a combination of resistance and endurance training.[27] Resistance training should be 2–3 times per week with 60–70% of maximum load, 1–3 sets each with 8–12 repetitions, and should be increased if undertaken in two successive sessions, to 13–14 repetitions where possible. Endurance training can include walking, cycling, or rowing and should be 3–5 times per week with an intensity of 60% of maximum load for 20–60 minutes.[27]

Question and Answer Session

Q: What would you like to see included in the next ERS statement on AATD?

Prof Chorostowska-Wynimko replied that screening is a key factor and a lack of screening means that many patients are misdiagnosed or have

delays in treatment initiation, and that a clear message to physicians should be to utilise screening techniques.

Prof Chapman commented that screening has been limited because previously there was no evidence for treatment efficacy. Following the results of the RAPID trials however, it should be mandatory for pulmonologists to screen and identify suitable patients so that they can begin timely treatment with A_1-PI therapy.

Prof Koczulla added that physical activity should be included as although there is a lack of evidence in AATD patients, there is a paucity of data in the COPD population.

Q: What type of patient is suitable for self-administration of intravenous A_1-PI therapy?

Prof Koczulla replied that patients must be able to cope with the task of administering an infusion and several checks would be necessary before implementing this system. Offering the appropriate training, as in other indications where self-administration is frequent, is of great importance. It will not be attractive to all patients alike. It may be an important option for patients with a long commute to their physician, however some patients may not be willing to undergo self-administration because the weekly visits to the clinic offer them a greater sense of security and a chance to socialise.

Q: There is a difference between the FEV_1 range given in the summary of product characteristics of the licensed products and also in the different treatment guidelines. Do you treat patients with FEV_1 >65% or <30%?

Prof Chapman replied that as previously discussed, the FEV_1 only partially reflects the disease process of progressing emphysema in patients with AATD. The new guidelines published this year recommend treatment if FEV_1 is <30% of the predicted value and to consider treatment for >65% when progressive disease is evident. This would be on-label treatment according to the summary of product characteristics for Respreeza.

Q: Do you think that there is a subgroup of patients who would benefit more from A_1-PI therapy?

Prof Chorostowska-Wynimko replied that clinical observation has demonstrated that there is a subpopulation of patients other than rapid decliners that would benefit more from A_1-PI therapy. However, such patients are difficult to characterise and it is a subjective observation.

Prof McElvaney added that although there is a reasonable amount of data on CT scans and FEV_1 measurements, there is a lack of data on DL_{CO} and other measurements and a need to further explore this to better phenotype patients.

Prof Chapman added that CT scan measurements were used in the RAPID trials and posed the idea of using lung density to track an individual patient rather than examining the subjective picture of emphysema on a CT scan and FEV_1 measurements. Lung density could be used to quantify and determine whether a patient is a rapid decliner over a period of 1 or 2 years.

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