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Review Article

A Review on the Self-Administration of Alpha-1 Antitrypsin Therapy

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Abstract

Augmentation therapy with human intravenous alpha1-proteinase inhibitors is the only specific treatment of pulmonary manifestations of Alpha-1 Antitrypsin Deficiency (AATD). The weekly intravenous administration of augmentation therapy in patients with AATD may impair quality of life; interfere with family, social, and leisure activities; and pose a challenge for school or work attendance. Self-administration of augmentation therapy is an alternative clinic-based administration that may increase patient satisfaction, self-care competence and independence. We review the experience with self-administration of intravenous drugs in other clinical conditions, the perceived advantages and barriers to self-administration of intravenous augmentation therapy, the clinical experience with self-administration of augmentation therapy, and the published recommendations for the implementation of self-administration of augmentation therapy in clinical practice. Self-administration is a very attractive option for many patients with AADT who desire to maintain or gain independence. Self-administration is easy to implement, providing the patients are properly selected and receive adequate training, and is associated with increased patient satisfaction.

Keywords: Alpha-1 antitrypsin deficiency; Augmentation therapy; Self-administration; Self-infusion independence; Satisfaction

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INTRODUCTION

Alpha-1 Antitrypsin Deficiency (AATD) is a hereditary metabolic disease characterized by serum Alpha-1-Antitrypsin (AAT) levels well below the normal range [1]. Although AATD is considered a rare disease, it is not as rare as other genetic disorders [2], with a prevalence at birth of 1/1,600-5,000 in Western Europe and the US [1]. This disease is associated with pulmonary morbidity, including the development of Chronic Obstructive Pulmonary Disease (COPD) and emphysema, and hepatic morbidity, such as the development of fibrosis and steatosis [3]. In addition, patients with AATD may exhibit other disorders, including neutrophilic panniculitis, Antineutrophil Cytoplasmic Antibody (ANCA)-associated vasculitis, chronic kidney disease, diabetes, and dyslipidemia [4]. AATD is associated with impaired quality of life, which is more marked in patients who develop COPD [3]. AATD is also associated with an important burden for caregivers, increased medical costs, and increased health care resource utilization [3]. Importantly, patients with AATD believe that more attention should be given to the social, psychological, and financial impacts of the disease [5].

The only specific treatment for pulmonary manifestations of AATD consists of the administration of exogenous AAT, called augmentation therapy, which has been demonstrated to reduce the progression of emphysema in randomized clinical trials [6, 7]. Although the evidence on usual treatments for COPD in patients with AATD is very limited, these treatments may not be as efficacious in treating AATD owing to important differences in the disease process [6]. According to international guidelines, augmentation therapy is indicated for individuals with AATD with an FEV1 less than or equal to 65%predicted and individuals with necrotizing panniculitis [8]; for those with AATD- associated pulmonary disease and an FEV1 greater than 65% predicted, the recommendation is to discuss with the individual and balance the potential benefits of reducing lung function decline with the cost of therapy and lack of evidence for such a benefit [8]. However, it is important to note that a recent observational study based on an international registry showed that augmentation therapy

has a beneficial effect on mortality, and this beneficial effect was not related to lung function as measured by FEV1 [9].

Regardless of the product, augmentation therapy with human Alpha1-Proteinase Inhibitors (A1PIs) requires intravenous administration of a once-weekly dose of 60 mg/kg [10, 11]. The weekly intravenous administration of augmentation therapy in patients with AATD may impair quality of life; interfere with family, social, and leisure activities; and pose a challenge for school or work attendance [5, 12]. In a survey conducted by the Food and Drug Administration (FDA) among 850 patients with AATD, they "emphasized the need for treatments that allow patients to pursue activities such as travel and social activities" [5]. In a study performed during the SARS-CoV-2 pandemic among 16 patients who were going to receive augmentation therapy on a home care basis, before initiating the program, all patients reported that augmentation therapy interfered much or very much with their life [13]. To overcome this limitation, there are two alternatives to augmentation therapy: Administration at home by a nurse and self-administration. While administration at home by a nurse has been shown to lessen the burden on the family and to improve the personal and family quality of life of patients with AATD [13], self-administration may further increase patient satisfaction and self-care competence [14, 15], which is supported by previous experience in other conditions, such as hemophilia and hereditary angioedema. Consequently, there is increasing interest and support from experts on the self-administration of intravenous AAT therapy in some patients with AATD [12, 16-18].

LITERATURE REVIEW

Self-administration of intravenous therapy in other conditions

An early 1991 report on thirty-seven patients with antibody deficiency who self-administered immunoglobulin infusion therapy reported benefits of this therapeutic strategy in terms of independence, convenience, comfort, and decreased disruption of activities and travel time [19].

Hemophilia is possibly the disease with the most experience on the self-administration of intravenous drugs. Self-management is considered essential for patients with hemophilia and also involves the administration of treatment products [20]. Unsurprisingly, in some countries, such as the Netherlands, most patients with severe hemophilia self-infuse prophylaxis [21]. These patients mostly begin learning self-infusion at the age of 12-13 years [21, 22], and although the learning process is as short as seven weeks [21], they become fully independent for self-infusion by the age of 17 years [22]. Similar experience has been reported in the UK [23]. In patients with hemophilia, self-infusion is associated with a perceived increase in independence, improved quality of life, and reduced interference with work or school activities [24, 25].

There is also important experience with self-administration in patients with hereditary angioedema. A 2006 report described the experiences of 31 patients with C1-INH deficiency with frequent, severe angioedema attacks who were trained to self-administer C1- inhibitor concentrate: 19 for on-demand treatment and 12 for prophylactic treatment [26]. The authors reported that all patients were successful in learning the technique and that the technical failure rate of self-injection was less than 2%. Moreover, patients on demand showed more rapid and effective treatment than in the situation prior to self-administration, and patients on prophylactic treatment showed a marked reduction in angioedema attacks from 4.0 to 0.3 attacks per month [26]. A small study of the experiences of seven patients showed that self-administration of intravenous C1-inhibitor therapy could improve both the physical and psychological components of quality of life, with patients gaining control of their disease and normalizing their work and family lives [27]. A more recent study in 20 patients with angioedema showed that the self-administration of intravenous C1-inhibitor therapy is safe and could be associated with improvements in quality of life and a reduction in health care resources and cost [28].

Self-administration of intravenous antibiotic therapy has also been attempted in several settings with promising results [29-32].

Perceived advantages and barriers to self-administration of intravenous AAT therapy

Despite the interest and support of experts on the self- administration of intravenous AAT therapy, the use of this therapeutic option in clinical practice has been very limited. A survey of patients with AATD included in the AlphaNet disease management and Prevention Program, a program created by a non-profit organization in the US to provide support and education on the disease, reported that among 555 responders, only 8% were self-administering AAT therapy [33]. Among those who had never self-administered, most did not consider self-administration, mainly because they were satisfied with their current regimen (80%) or because of a lack of confidence (26%). Interestingly, 44 patients using self-administration reported being very satisfied (95%) or satisfied (5%) with their regimen; most (84%) reported no

difficulties, and 93% considered that gaining greater independence was the greatest benefit [33].

A largest survey conducted in 2022 among 5,266 participants in the disease management program of AlphaNet shows a global picture of the practice of self-administration in the US [34]. As in the previous survey, only 8% of the individuals were on a self-administration regimen, approximately 40% used permanent intravenous catheters, and 60% used peripheral intravenous catheters. In the remaining participants, AAT was administered by a nurse at home (60%) or at a clinic (31%). Participants who self-administered were younger and more likely to receive weekly infusions than those on clinic-based administration and were more likely to be very satisfied with their infusion choice (93%) than were those in clinic-based (73%) or home- based (86%) administration. The most frequently perceived advantages of self-infusers were freedom and flexibility (78%), ability to travel (45%), avoidance of infusion clinics, and time savings (36%). Among those who had never self-infused, the perceived advantage of self-infusion was also flexibility (89%), which allowed travel (44%). Three-fourths of self-infusers had no concerns about self-infusion; the most frequent concern was venous access, and the most frequent challenge was finding veins. Among former self-infusers, the most common reasons for stopping home infusion were a lack of insurance coverage (25%), difficulty with venous access (15%), and difficulty with the port (14%). Finally, 81% of the never infusers reported that they would not consider self-infusion, mainly because of a lack of confidence (63%) and because they were currently satisfied with their regimen (56%).

Therefore, the perceived advantages of self-administration of AAT therapy are clear and can be summarized in one word: Independence. A major barrier seems to be a lack of confidence. Importantly, in the AlphaNet survey, participants reported that the first mention of AAT self-administration was by physicians (33%) or nurses (28%) [34]. Therefore, it is likely that a major barrier to a greater acceptance of self-administration is the lack of information on the advantages and disadvantages of this treatment modality. This situation leads to experts recommending increased awareness among patients and physicians on the self-administration of AAT therapy and that the development of guidelines and training programs could contribute to that end [17, 33].

Finally, it is important to mention that only one product for AAT therapy (Respreeza®) [10] is allowed for self-administration on its label (according to the summary of product characteristics, first infusions should be administered under the supervision of a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency, and subsequent infusions can be administered by a caregiver or by the patient). In our view, this is also a barrier to expanding the use of self-administration.

Clinical experience with self-administration of AAT therapy

The above mentioned surveys provide almost no information on the clinical results of the self-administration of AAT therapy. The only information available is derived from case reports.

Herth, et al., reported the experience of a 52-year-old woman with severe AATD and bronchiectasis that was successfully managed through the self-administration of 60 mg/kg AAT therapy (Reespreza®) on a weekly basis. The author did not provide the reason for the use of self-administration but reported several perceived benefits, such as a reduction in exacerbation frequency; improved independence, quality of life, and disease awareness compared to health care professional-based administration; a reduction in time spent in treatment compared to hospital-administered AAT; and flexibility [17].

We recently reported our experience with the self-administration of AAT therapy in two patients [35]. The first patient was a 50-year-old woman who was employed full-time and practiced sports daily. She complained of dyspnea grade 1, had a predicted FEV1 of 58.6%, had panacinar emphysema on computed tomography, and was diagnosed with COPD with exacerbations. Genetic testing revealed the genotype Pi*ZZ and an A1PI level of <20 mg/dL. We initiated treatment with Long-Acting β2-Agonists (LABA), Long-Acting Muscarinic Antagonists (LAMA), and, after adequate training, self-administration of AAT therapy (Respreeza®). Self-administration was proposed and accepted to maintain independence. At the time of the report, the patient had been on a self-administration regimen for 9 months without complications, except for blood reflux in the catheter that was resolved by phone with the help of the clinic staff. At the last follow-up visit, the patient had dyspnea grade 0, a predicted FEV1 of 65%, no exacerbations, and a serum A1PI of 68 mg/dL. She reported no interference with her regular physical activity, full-time work, or travel.

The second patient was a 68-year-old male diagnosed with COPD, with dyspnea grade 1 and a CT scan showing panacinar emphysema, who experienced a worsening of lung function 3 years after diagnosis, with a predicted FEV1 of 60% [35]. The genotype was Pi*ZZ. The patient initiated AAT therapy (Prolastin®), which should be administered by a health care professional according to its label [11]. During the COVID-19 lockdown and due to the fear of being infected, the patient

discontinued AAT therapy, and although he maintained COPD treatment, 6 months later, he experienced severe hypoxemia and a predicted FEV1 of 52%. Therefore, after training with a nurse, the patient initiated self-administered AAT therapy (Respreeza®). At the time of the report, 32 months after initiating self-infusion, the patient had grade 2 dyspnea, a predicted FEV1 of 55%, and an oxygen saturation of 95%. He did not report incidents or adverse events during self-infusion and reported that self-administration allowed him to travel for social activities.

A study is currently underway to assess the effectiveness of a home self-administration learning program in terms of switching to self- administration (Respreeza®) and long-term maintenance of this administration (ClinicalTrials.gov Identifier: NCT04262284). The estimated completion date is March 2025.

DISCUSSION

Recommendations for the implementation of self- administration in clinical practice

Some recommendations for the implementation of self- administration have been issued [17, 36], but possibly the most complete recommendations have been published by Torres-Duran, et al., [36]. These authors include recommendations on the selection of patients for self-administration, the role of health care professionals in this process, the training of patients and several other issues, including follow-up, adherence, and patient support [36]. Interested readers can find detailed information on that publication. However, after a brief review we considered two key issues: Patient selection and training. For the selection of patients, social and clinical criteria should be taken into account [36]. From a social perspective, patient motivation and commitment are key issues. Initially, candidates are those who express their desire to improve their quality of life, achieve greater independence or flexibility, and/or avoid visiting the hospital center. However, in our view, in the context of a patient-centered approach (i.e., in which an individual's specific health needs and desired health outcomes are the driving force behind all health care decisions [37]), all patients initiating treatment with AAT therapy should be informed of the alternative regimens that are available in their setting (i.e., clinic-based, home-based with nurse, or self-administration). Patients should be committed in adhering to the training program and the overall physician's recommendations. From a clinical perspective, the patient should be hemodynamically stable, exhibit psychological stability to ensure adherence to the procedures and treatment, and have the potential ability to perform canalization (e.g., cognitive ability and dexterity).

As mentioned above, the major barrier to the use of self- administration is the lack of confidence and the major issues when self-administration is used have to do with vein access. Therefore, training on the appropriate technique for intravenous infusion and follow-up of those candidates who select a self-administration regimen are the basis of success. After training, it is also recommended for patients to perform first self-infusions at the clinic with the supervision of a nurse and, if possible, to maintain a close follow-up during the first self-infusion at home [36].

CONCLUSION

Self-administration of intravenous drugs has been successfully implemented in other diseases, such as hemophilia or hereditary angioedema. Self-administration is a very attractive option for many patients with AADT who desire to maintain or gain independence. Self-administration is easy to implement, providing the patients are properly selected and receive adequate training, and is associated with increased patient satisfaction.

CONFLICT OF INTEREST

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