Use of dornase alfa in cystic fibrosis: an Audit of Italian specialists

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Abstract

Background: The goal of mucoactive therapies in cystic fibrosis (CF) is to enhance sputum clearance and to reduce a progressive decline in lung function over the patient's lifetime. We aimed to investigate the level of consensus among specialists from Italian CF Centers on appropriateness of therapeutic use of dornase alfa (rhDNase) for CF patients. Method: A consensus on appropriate prescribing in CF mucoactive agents was appraised by an online Delphi method, based on a panel of 27 pulmonologists, coordinated by a Scientific Committee of six experts in medical care of patients with CF. Results: Full or very high consensus was reached on several issues related to therapeutic use of dornase alfa for CF patients in clinical practice. Conclusions: Modified Delphi method was used to define the most appropriate use of dornase alfa in routine CF to improve lung function and long-term outcomes in patients, in agreement with international guidelines on CF management.

1. Introduction

Impaired mucociliary clearance characterizes lung disease in cystic fibrosis (CF). In CF patients, the alteration of the cystic fibrosis transmembrane conductance regulator (CFTR) results in defects of the electrolytes transport, which then cause increased water reabsorption across respiratory epithelia[1,2]. This may induce dehydration of the airways' surface liquid which may prevent normal mucus clearance. In the airways, alterations of the ionic transport lead to the production of thick secretions with obstruction of the glandular ducts and progressive epithelial damage. In pediatric CF patients, recurrent bacterial infections and chronic colonisations induce persistent inflammatory response, progressive fibrosis with loss of lung parenchyma function[3,4].

Purulent pulmonary secretions of individuals with cystic fibrosis contain very high concentrations of extracellular DNA released by degenerating leukocytes that accumulate in response to these infections[5].

Cystic fibrosis is characterized by a progressive decline in lung function over the patient's lifetime and by a chronic inflammation in the pulmonary tissues. The cycle of chronic obstruction, infection, and inflammation ultimately contributes to the occurrence of respiratory failure, which accounts for more than 80% of mortality in patients with CF[6]. Therefore, most patients require mucoactive agents and additional therapeutics that target downstream manifestations of the disease.

Strategies to enhance sputum clearance are a major therapeutic aim in CF and treatment with dornase alfa has been widely accepted to be of benefit[7]. Hydrolyzing the DNA in CF patients' mucus and reducing sputum

viscoelasticity, this mucoactive agent is effective in reducing the decline in lung function and decreasing the number of pulmonary exacerbations[8].

Despite the inclusion of dornase alfa in the recommended therapies for CF, databases managed by the main Cystic Fibrosis Societies show that significant differences exist between countries in its prescription for CF treatment in current clinical practice.

In the United States, according to the Cystic Fibrosis Foundation (CFF) Patient Registry, dornase alfa was used by the vast majority of individuals with CF (87%) in 2017[9]. These use rates of dornase alfa are much higher than those observed in the same period of time in European countries. Italy, Spain, Sweden and some eastern countries, are among countries with the lowest use of this mucoactive agent in Europe. Indeed, the most recent Patient Registry Annual data report of the European Cystic Fibrosis Society (ECFS) shows that in 2017 the use rates of dornase alfa, seen in all CF patients, were 33% in Italy and 62% in United Kingdom[10].

Considering the current scenario of dornase alfa use in different geographic areas, the aim of this multicenter work was to investigate the level of consensus among specialists from Italian CF Centers on appropriateness of therapeutic use of dornase alfa for CF patients. Indeed, the evidence of how the Italian CF experts are dealing with the use of dornase alfa may contribute to expand the global discussion within the international scientific community on factors that influence the prescription of mucolytic agents in CF clinical practice.

Therefore, our final goal was to promote the most appropriate use of dornase alfa to improve lung function and long-term outcomes in people with CF, in alignment with recommendations of the international pulmonary guidelines.

2. Methods

To assess the consensus on the appropriateness of therapy with dornase alfa for CF patients, we used an online Delphi-based method (Estimate-Talk-Estimate)[11]. This is a group-facilitative method designed to verify the convergence of opinion of a panel of experts in a given area of uncertainty within health-related research. The experts have to complete anonymously a series of structured questionnaires anonymously in order to reach the most reliable group consensus according to both evidence and individual experience. By completing and returning the questionnaire, each participant consented of be involved in the study.

The process was developed over nearly seven months by the following steps: (i) establishment of a scientific steering committee of six experts who were in charge preliminarily of reviewing the literature and then of developing the statements to be ranked; (ii) selection of an expert panel of specialists; (iii) online statement ranking by each expert; (iv) collection and analysis of the results; (v) final consensus meeting.

Scientific steering committee

Six experts were identified among Italian institutions, as representative of specialists involved in medical care of patients with CF. The scientific steering committee defined 11 statements divided into the following seven main topics:

1. Identification of the patient to be treated with mucoactive agents
2. Identification of the pediatric patient to be treated with mucoactive agents
3. Definition of outcomes indicative of clinical benefit
4. Criteria for choosing mucoactive agents
5. Manageability of therapy with mucoactive agents
6. Strategies to improve therapeutic adherence
7. Physiotherapist's role in managing therapy

Panel of CF specialists

Nineteen experts were selected from 16 specialized Centers as representative of the clinical practice in the field of CF management in Italy (1. Ospedale Civile S. Liberatore, Atri; 2. Ospedale San Carlo Di Potenza;

3. Ospedale Di Lamezia Terme; 4. Azienda Ospedaliero-Universitaria di Parma; 5. Ospedale Pediatrico Bambino Gesù, Roma; 6. Policlinico Umberto I, Roma; 7. Presidio Ospedaliero G. Salesi, Ancona; 8. Azienda Ospedaliero-Universitaria S. Luigi, Orbassano; 9. Ospedale Universitario di Messina; 10. Ospedale Dei Bambini G. Di Cristina, Palermo; 11. Azienda Ospedaliera Meyer, Firenze; 12. Presidio Ospedaliero Alto Chiascio, Gubbio; 13. Ospedale Civile Maggiore, Verona - Centro Pediatrico; 14. Università degli Studi di Napoli "Federico II" AOU, Napoli; 15. Presidio Ospedaliero Maggiore Policlinico, Milano; 16. Istituto G. Gaslini, Genova).

Online statement ranking

The 11 statements developed by the steering committee were delivered to panel experts who rated agreement or disagreement for each of them, independently and blindly. The survey was performed online on a secured survey website, using an online dedicated platform: "Pulmocare Team". The scientific steering committee collected and analyzed the results prior to the final consensus meeting.

Participants expressed their level of agreement on each statement using the RAND nine-point scale (ranging from *1 = completely disagree* to *9 = completely agree*) and consensus was reached that a statement had to be considered appropriate if the median score was greater or equal to 7.

Final consensus meeting

The final phase of the project was based on the Consensus Development Conference method[12,13]. After the individual and anonymous online survey, an expanded panel (28 CF specialists), plus the six members of the steering committee, attended a web meeting and used in order to express their opinion on each statement using two response options (1=yes, 2=no) with final consensus defined at [?] 80% agreement.

3. Results

The panel of CF specialists performed rated agreement or disagreement for each of the 11 statements regarding different issues related to the prescribing process of mucoactive agents, including dornase alfa, for the management of CF patients.

TOPIC 1: Identification of the patient to be treated with mucoactive agents

Statement 1*: Treatment with mucoactive agents should be proposed at the first evidence of pulmonary involvement in order to prevent or slow the decline in lung function through indirect control of inflammation, with reduction of mucus accumulation and, consequently, of the infectious process.*

The expert panel reached consensus on starting the use of mucoactive agents in CF patients at the first evidence of pulmonary involvement(**Figure 1A**). In final consensus meeting, there was no unanimous response to this statement.

The pathophysiology of CF is characterized by a continuous cycle of obstruction, infection, and neutrophil-dominated inflammation[14]. In addition, necrosis of neutrophils leads to the accumulation of extracellular DNA and actin, increasing the viscosity of mucous and producing further obstruction. Reduction of high molecular weight DNA into smaller fragments by using dornase alfa has been proposed as a treatment to reduce the mucus viscosity and improve mucus clearance from obstructed airways in CF patients[15].

Given the role of the inflammatory process as a driver of irreversible lung destruction, there is an increasing interest in therapies with anti-inflammatory effects to slow disease progression when used early in the course of disease[16]. Dornase alfa has well-documented beneficial clinical effects on the obstruction and infection components of the disease process and has also shown positive effects on markers of inflammation[16].

Dornase alfa was shown to exhert a beneficial effect on metalloproteases in BAL fluid of patients with CF, supporting the positive impact of this mucoactive agent on airway inflammation in CF[17]. In particular, a randomized trial including 105 CF patients with mild lung disease (FEV_1 >80% predicted) demonstrated this potential anti-inflammatory effect. Based on an initial bronchoalveolar lavage, patients were divided into two groups, those with airway inflammation and those without. CF patients with inflammation were

then randomized to treatment with dornase alfa or not. In patients treated with dornase alfa, there was no change in inflammatory responses as measured by elastase and IL-8 levels and neutrophils number.

CF patients not treated with dornase alfa and patients who did not have inflammation at baseline all had worsening neutrophilic inflammation on follow-up. In addition, in treated patients FEV_1 dropped by 1.99% predicted per year, as compared to a 3.26% predicted drop per year in patients not treated with dornase alfa1[7].

Statement 2: *Treatment with mucoactive agents should be proposed in patients with CF with frequent pulmonary exacerbations of lung disease.*The complete agreement of the expert panel on this statement is relevant as it shows that the frequency of exacerbations is considered a marker for the use of mucoactive therapy (**Figure 1B**).

In final consensus meeting, there was no unanimous response for this statement.

A recent Cochrane review of randomized and quasi-randomized controlled trials comparing dornase alfa to placebo, standard therapy or other medications that have a positive impact on airway clearance, showed that compared with placebo, therapy with dornase alfa improved lung function in people with CF in trials lasting from one month to two years and led to a decrease in pulmonary exacerbations in trials of six months or longer[18].

TOPIC 2: Identification of the pediatric patient to be treated with mucoactive agents

Statement 3*: In children with CF without evidence of lung disease, treatment with mucoactive agents should be considered in the presence of early pulmonary abnormalities documented by imaging or tests of pulmonary function, including LCI.*

Although in final consensus meeting, there was no unanimous response to this statement, the high level of agreement reached on this aspect regarding the appropriateness of the mucoactive agent prescription in pediatric patients with CF, as shown in **Figure 1C,** may be related to the importance attributed to the role of airway inflammation in the progression of CF in children without evidence of pulmonary disease[19].

In children with CF without evidence of lung disease, in the presence of early pulmonary changes documented by instrumental examinations, starting the mucoactive therapy early is important in order to act on the component of inflammation and obstruction, anticipating the cascade of pathological events that self-maintains in CF. Amin and collaborators demonstrated that the lung clearance index (LCI) is a sensitive and responsive outcome measure that was able to detect a significant treatment effect from dornase alfa in a pediatric cohort with mild lung disease and normal spirometry[20].

Importantly, a two-year randomized, placebo-controlled trial of dornase alfa in young CF patients with mild lung function abnormalities demonstrated that this therapy maintains lung function and reduces the risk of exacerbations[21]. At 96 weeks, patients treated with dornase alfa maintained FEV_1 at their baseline value (mean change from baseline +- SE, 0.04% +- 0.8% predicted), whereas patients receiving placebo had a mean decrease from baseline of 3.2% +- 0.8% predicted. Thus, the treatment benefit for FEV_1 in patients who received dornase alfa was 3.2% +- 1.2% predicted ($P = 0.006$). The risk of respiratory exacerbations was reduced by 34% in patients receiving dornase alfa (relative risk 0.66, $P = 0.048$). The results of this two-year trial support the importance of an early intervention approach in children with CF[21].

TOPIC 3: Definition of outcomes indicative of clinical benefits

Statement 4*: The main outcomes to be evaluated in order to assess the beneficial effects of mucoactive therapy in patients with CF include pulmonary function, frequency of pulmonary exacerbations and quality of life.*The Italian experts in CF, in agreement with the most recent guidelines on the management of CF patients, suggest to assess respiratory function, frequency of pulmonary exacerbations and quality of life which represent the main outcomes for establishing the clinical effectiveness of mucoactive therapies (**Figure 2**)[22,23]. In final consensus meeting, there was unanimous response to this statement. The NICE guidelines

indicate that inflammation markers, the need for antibiotics for exacerbations and adverse events should also be considered[22].

Pulmonary exacerbations are critical events throughout the lifetime of CF patients and may not be fully reversible[24]. Frequent exacerbations are associated with accelerated decline in lung function[25]. Poor lung function and pulmonary exacerbations in the past 6 months have been related to poor health related quality of life (HRQL)[25-27]. The Cystic Fibrosis Questionnaire-Revised (CFQ-R) is a validated patient reported outcome measure of HRQL specifically designed for patients with CF[28,29]. This disease-specific instrument may be utilized in clinical trials to assess the effects of new therapies, to document the progression of disease, and to inform clinical practice[28].

TOPIC 4: Criteria for choosing mucoactive agents

Statement 5*: The main criteria for guiding the choice between the different mucoactive agents should be the patient's age; the mechanism of action of mucoactive agent and the patient's clinical conditions.*

The expert panel reached consensus on the main criteria for choosing between different mucoactive therapies. Experts did agree that different mucoactive drugs are characterized by different mechanisms of action and intervene at various levels of the pathogenetic cascade of CF. Therefore, the mechanism of action of the mucoactive agent together with the age and the patient's clinical conditions are key factors in the decision making in CF (**Figure 3A**). In final consensus meeting, there was unanimous response to this statement.

Mucoactive drugs are able to modify the properties of mucus and promote the muco-ciliary clearance which is impaired both by mucus viscoelasticity and by mucus adhesiveness[30].

A European consensus document reviewed in detail therapies for CF, concluding that modes of action of hypertonic saline and dornase alfa differ and therefore the two drugs cannot replace each other. In addition, the use of any mucoactive agent should be recommended for CF patients according to age[31].

Statement 6*: In CF patients with evidence of lung disease, dornase alfa should be preferred to other mucoactive agents, in order to achieve long-term stabilization/improvement of lung function.*

The experts reached consensus also on the choice of dornase alfa as the most appropriate mucoactive agent in CF patients with evidence of lung disease (**Figure 3B**). In final consensus meeting, there was unanimous response for this statement.

According to the most recent version of the European CF Society (ECFS) document on standard of care, the only mucus degrading agent that has proven efficacy in CF is dornase alfa[32]. The authors reached this conclusion after performing a systematic review of available evidence. Studies demonstrated improvements in lung function and a reduction in pulmonary exacerbations in patients regardless of disease severity.

In addition, evidence from an analysis of a large database suggests that dornase alfa reduces lung function decline[33].

Statement 7*: In CF patients with inadequate response or intolerance to dornase alfa therapy, the use of the combination of dornase alfa and hypertonic solution or hypertonic solution alone should be considered .*

Italian CF experts reached consensus also on this statement in light of the different mechanisms of action of the different mucoactive agents (**Figure 3C**). In final consensus meeting, there was unanimous response for this statement.

Mucoactive drugs fall into two categories, either mucolytic or hyperosmolar. Dornase alfa, a mucolytic agent, and hypertonic saline and mannitol, both hyperosmolar agents, have all been shown to benefit CF patients.

Dornase alfa reduces the viscoelasticity of sputum by breaking down DNA released by neutrophils which flood into infected airways in a fruitless attempt to clear the airway lumen of infecting bacteria[34].

Nebulised hypertonic saline in CF treatment is available at a concentration of 3% to 7% sodium chloride. Increasing salt concentrations on the luminal side of the respiratory epithelium is thought to hydrate the

viscous mucus, thereby improving mucociliary clearance and hence lung function[31,35,36].

Mannitol, an alternative hyperosmolar therapy, when inhaled, draws water into the airways by creating an osmotic gradient and has been shown to increase mucociliary clearance in CF and other obstructive airways diseases[37-39].

In conclusion, the mechanism of action of hyperosmolar agents differs from that of dornase alfa and both approaches are complementary in improving mucus clearance in patients with CF[40].

Careful assessment of the appropriateness of a mucoactive therapy must take place not earlier than six months after its initiation. Accurate assessment, discussion and monitoring will help to choose guiding the most appropriate agent or combination of agents for each patient with CF.

TOPIC 5: Manageability of therapy with mucoactive agents

*Statement 8***:** *Dornase Alfa therapy has important advantages in terms of handling and tolerability, with potential positive impact on therapeutic adherence.*

The high consensus reached on this statement has to be correlated to the well-known tolerability profile of dornase alfa (**Figure 4**). In final consensus meeting, there was unanimous response to this statement.

Cystic fibrosis is a chronic and progressive disease and needs multiple life-long therapies that require daily and time-consuming administration. The treatment burden of CF raises the question of medication adherence.

Observational studies originating from registries confirmed that CF patients using dornase alfa benefit from its use and that the tolerability and safety profile of the drug in all age groups are good[41]. After completion of the Epidemiologic Registry of Cystic Fibrosis (ERCF) project, a comprehensive safety analysis of dornase alfa was performed. Emphasis was placed on infants and children under 5 years of age. The ERCF database contained data on 15,979 patients who were enrolled between 1994 and 2000. Twenty-eight out of 15,865 (0.18%) serious adverse events (SAEs) occurring during total ERCF follow up were classified by the participating clinics as possibly related to dornase alfa and most of these SAEs were typical complications of CF[39]. Patients under 5 years of age who were treated with dornase alfa experienced a similar frequency of adverse events resulting in hospitalization or other serious outcomes during treatment as in off-treatment periods[41]. These results indicate that CF patients under 5 years of age tolerate dornase alfa at least as well as older patients and support the evidence from previous RCTs that infants and young children may benefit from this therapy[42,43].

In clinical practice, several factors contribute to a better management of dornase alfa therapy than therapy with hypertonic solution by CF patients. Indeed, dornase alfa is administered once a day and it is not necessary to perform a pre-use test or pharmacological protection which are required before administering other mucoactive agents. The onset of cough, which is very common with hypertonic solution and mannitol, is never reported during the use of dornase alfa. In addition, irritative symptoms are rare with dornase alfa and the drug is completely tasteless.

Good tolerability of dornase alfa therapy, minimum treatment burden and time requirement play more important roles in medication adherence[44,45].

TOPIC 6. Strategies to improve therapeutic adherence

Statement 9*: Adherence to recommended treatment regimen is crucial to ensure the effectiveness of therapies. Consequently, it is important to identify the specific barriers to therapeutic adherence in CF patients, planning intervention strategies based on specific needs .*

All CF experts agreed that it is necessary to sustain therapeutic adherence which represents a very important factor in achieving beneficial effects from therapies in CF patients (**Figure 5A**). In final consensus meeting, there was unanimous response to this statement.

Mucoactive therapies to augment mucociliary clearance and to control infection and inflammation are prescribed as maintenance therapies to improve lung function and prevent pulmonary exacerbations. Despite the benefits of CF treatments, medication adherence among individuals with CF remains low, ranging from 33% to 76%[46-48]. Adherence of CF adults to medication regimens has been documented as problematic[49,50].

Poor adherence to medication is associated with adverse clinical outcomes in CF[51].

Adherence to recommended treatment regimen is influenced by the extent of treatment burden, having the time to do treatment, having a routine, forgetting to do therapy, a person's identity, perceptions of control, social support, and knowledge and interaction with health professionals[52].

Completely understanding the factors affecting adherence is a crucial step in the process of developing effective evidence-based behavior change interventions to support self-management of long-term conditions. A recent study emphasizes that different people have different issues affecting adherence including issues of motivation, capability, and opportunity. Consequently, there is no simple one-size fits all intervention that can be effective, and clinicians need to be aware of these differences in order to tailor adherence support appropriately[52].

Statement 10*: The motivational interview with patients could be used to improve therapeutic adherence and, consequently, disease management .*

The expert panel reached a high level of consensus on the use of the motivational interview as a strategy to enhance adherence in cystic fibrosis (**Figure 5B**). In final consensus meeting, there was unanimous response to this statement.

In a very complex disease such as cystic fibrosis, the relationship between patient and health professional is extremely relevant and should allow for good communication and mutual respect[53].

To enhance adherence clinicians should be mindful that in a condition where treatment burden and time pressures are huge, any interventions should focus on simplifying care and reducing treatment burden. CF specialists should establish a supportive, collaborative relationship with patients and their families. Indeed, open and honest dialogue may reveal barriers to the adherence, such as financial, psychiatric, or social stressors that may require referral to a psychologist, or team social worker for assistance[54]. Patient-centered, collaborative approaches to consultations and management are increasingly being viewed as desirable models of care.

Motivational interviewing (MI) was first described in 1983, as a patient-centered counseling style developed specifically to help patients change behavior[55]. Clinicians and other healthcare professionals practicing MI support CF patients to explore discrepancies between beliefs and behaviours and move towards change by using active listening strategies[56,57].

TOPIC 7: Physiotherapist's role in managing the therapy

Statement 11*: A physiotherapist with a specific expertise in respiratory rehabilitation should be part of the multidisciplinary team in order to define the most appropriate therapeutic strategy for the individual patient.*

A very high consensus was reached by the expert panel on this statement (**Figure 6**). In final consensus meeting, there was unanimous response to this statement. The respiratory rehabilitation program for CF patients often includes aerosol therapy, the management of which is also the responsibility of the physiotherapist and not just the clinician.

It is now widespread opinion that CF patients should be cared for by physiotherapists with an appropriate level of expertise in CF management and there should be adequate staffing levels to maintain these standards of care. The physiotherapist represents a valid interface both for the clinician and for the patient who often feels freer and more uninhibited in reporting doubts and uncertainties related to therapies.

The findings of an Italian survey indicated that physiotherapists play a key role in the care of Italian CF patients, by performing inhaled therapies and educating patients and families to their use[58]. Most physical

therapists actively participate and provide hands-on demonstrations to patients and caregivers[58].

These data are coherent with the role of physiotherapists involved in the respiratory care of cystic fibrosis as outlined in the ECFS standards of care[59]. The CF physiotherapist should also implement strategies for the management of complications or comorbidities experienced by the ageing patient[59]. All interventions should be tailored to the individual patient, with consideration of his age, severity of disease, physical side-effects or complications, and social and domestic conditions[59].

5. Conclusions

This document is the result of an Italian multicenter work aimed at optimizing the use of dornase alfa in CF clinical practice starting from the analysis of factors that influence the current varied scenario regarding its use in CF centers.

In agreement with international guidelines on CF management, we suggest treating CF patients with mucoative agents at the first evidence of pulmonary involvement in order to prevent or slow the decline in lung function and decrease the number of pulmonary exacerbations.

In the pediatric setting, we stress the importance of making a concerted effort to establish early lung abnormalities by imaging and sensitive pulmonary function tests in children and to start timely treatment with mucoactive agents.

When selecting mucoactive agents it is important to consider the age, the clinical conditions of the patient and the mechanism of action of mucoactive agents. Due to its unique features, dornase alfa should be more taken into consideration, dornase alfa has significant therapeutic benefits regardless of the CF patient's disease severity and enables long-term stabilization/improvement of lung function. In addition, dornase alfa therapy has important advantages in terms of handling and tolerability, with a potential positive impact on therapeutic adherence. Careful assessment and monitoring of individuals with cystic fibrosis will help choose the most appropriate mucoactive medication or combination of mucoactive medications.

When possible, the care of CF patients should be carried out by a multidisciplinary group of specialists including a physiotherapist of respiratory rehabilitation in order to define the most appropriate therapeutic strategy for the individual patient. The CF care team should also discuss with patient and develop an appropriate treatment plan for him.

DECLARATIONS

Conflict of interest

Giovanni Pappagallo, Vincenzo Carnovale, Carla Colombo, Valeria Raia, declare that they have no conflict of interest.

Dr. Blasi reports grants and personal fees from AstraZeneca, grants from Bayer, grants and personal fees from Chiesi, grants and personal fees from GSK, personal fees from Grifols, personal fees from Guidotti, personal fees from INSMED, grants and personal fees from Menarini, personal fees from Mylan, personal fees from Novartis, grants and personal fees from Pfizer, personal fees from Zambon, personal fees from Vertex, in the last three years outside the submitted work.

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Author contribution statement

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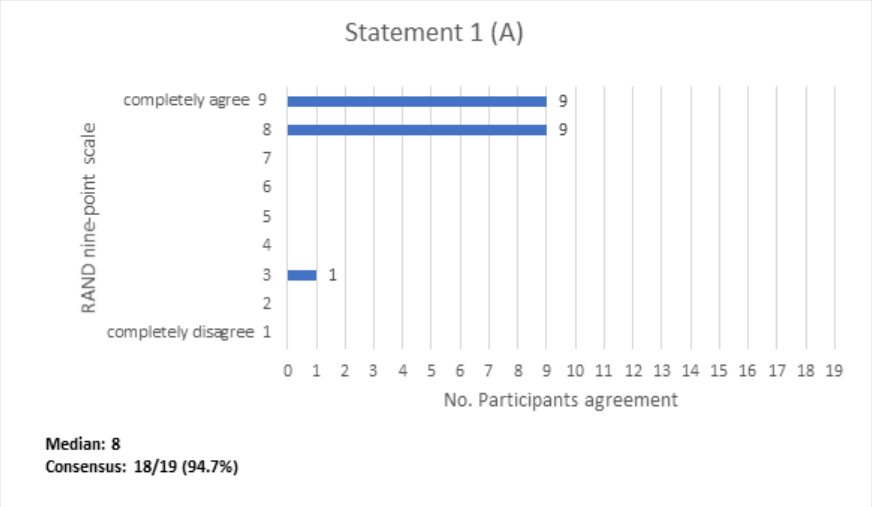
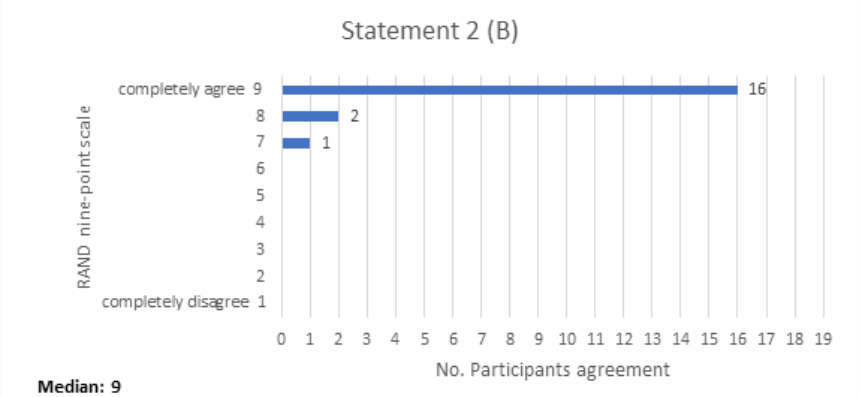
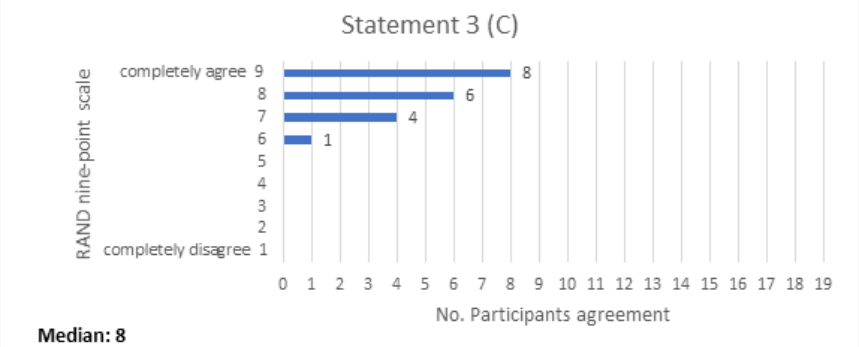


Median: 8
Consensus: 18/19 (94.7%)



Median: 9
Consensus: 19/19 (100%)



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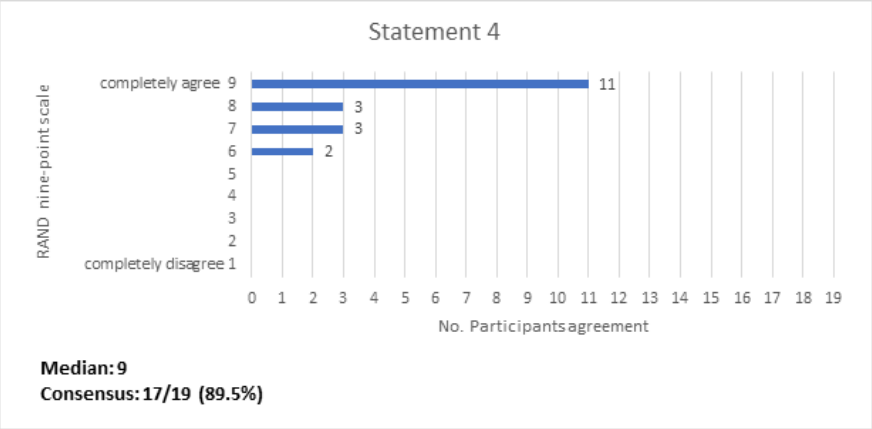
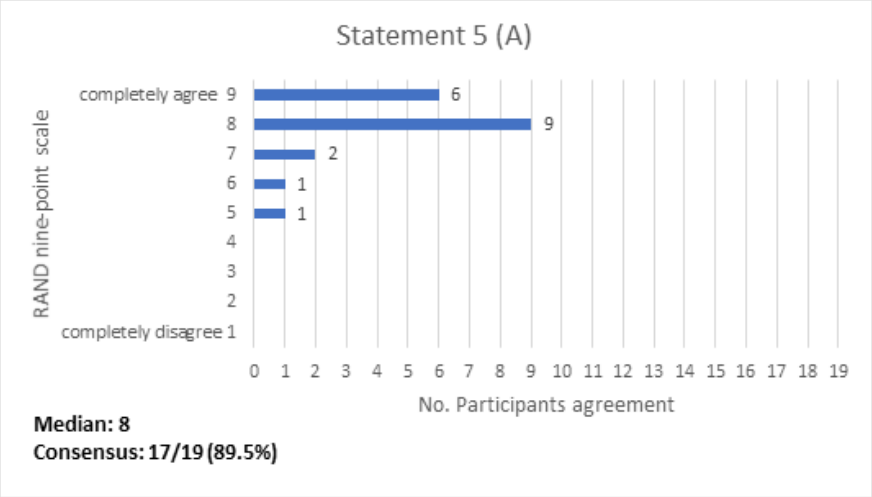
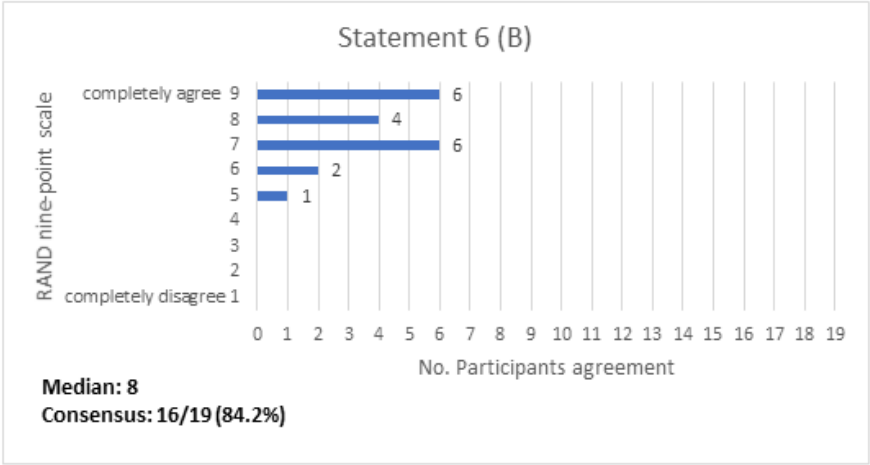
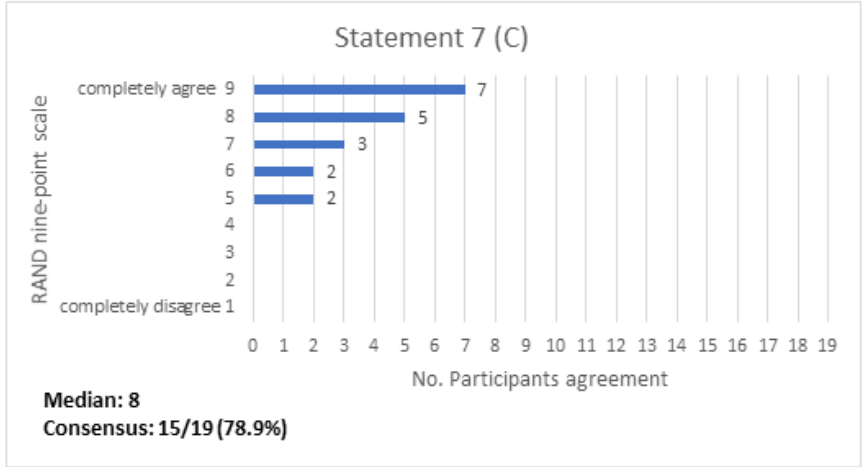




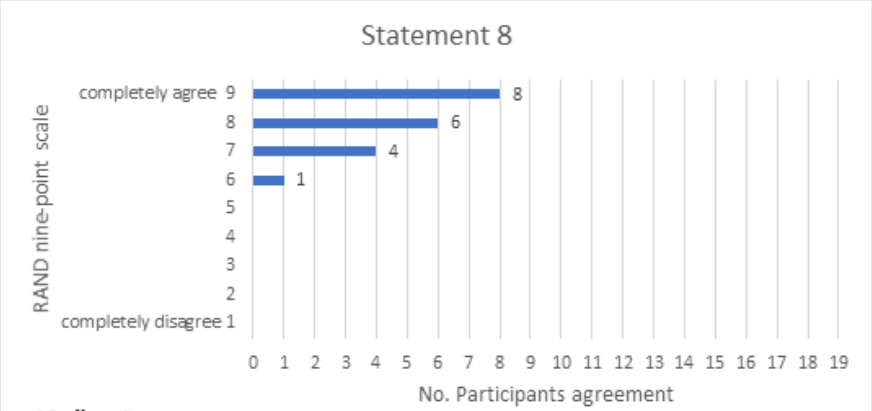
Median: 8
Consensus: 17/19 (89.5%)



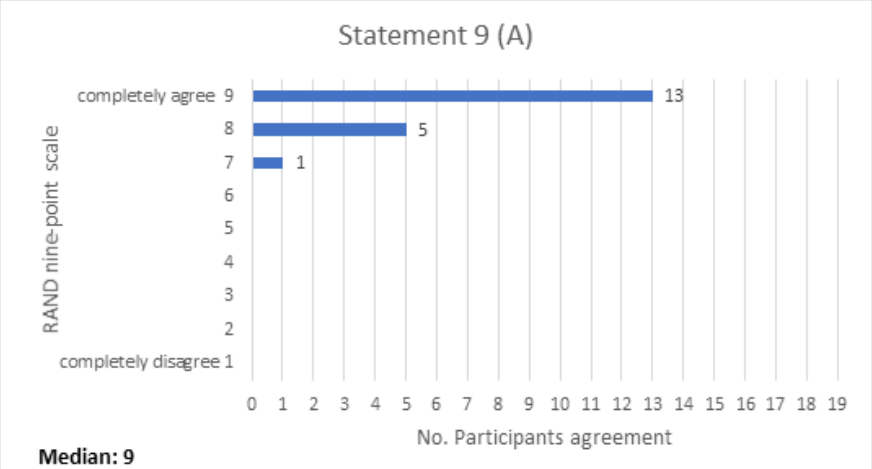
Median: 8
Consensus: 16/19 (84.2%)



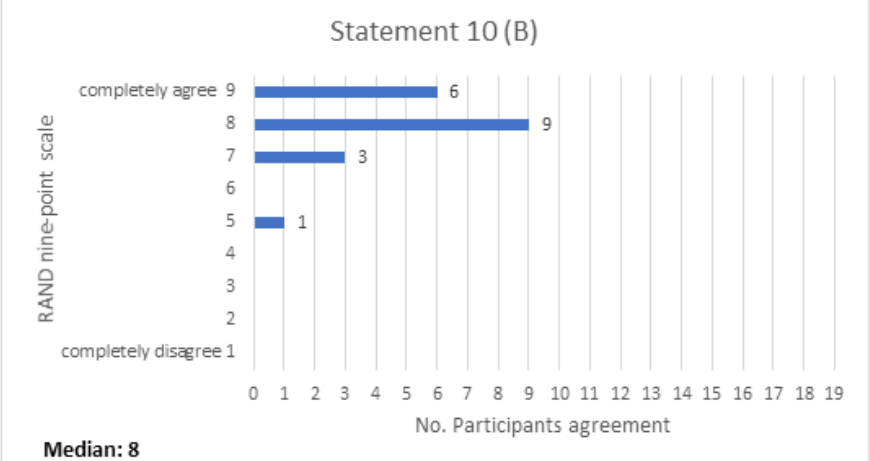
Median: 8
Consensus: 15/19 (78.9%)



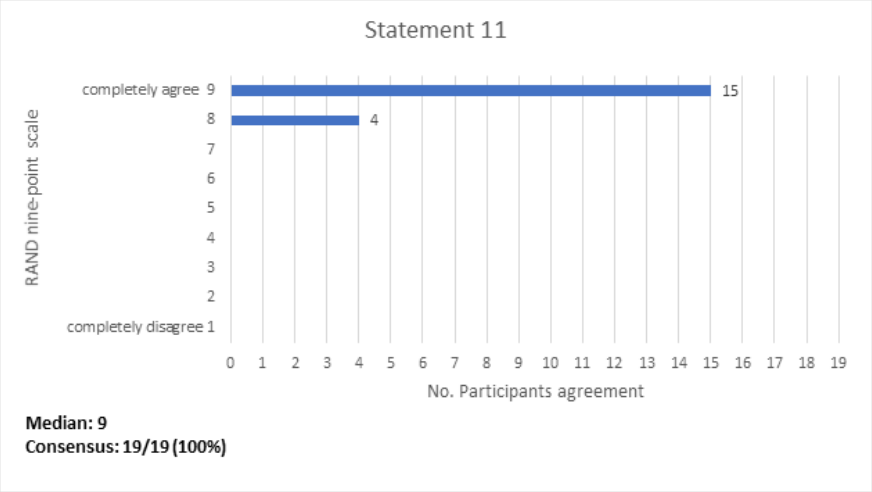
Median: 8
Consensus: 18/19 (94.7%)



Median: 9
Consensus: 19/19 (100%)



Median: 8
Consensus: 18/19 (94.7%)



Median: 9
Consensus: 19/19 (100%)