Delphi consensus on the current clinical and therapeutic knowledge on Anderson-Fabry disease

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Abstract

Background: Despite the growing interest in Anderson Fabry disease, uncertainties in terms of disease management remain, particularly practical details on use of approved enzyme replacement therapy. We report the results of a Delphi consensus panel on the management and therapeutic aspects of Fabry disease.

Methods: A survey designed to gauge consensus among experts involved in the diagnosis and treatment of Fabry disease with agalsidase alfa, was compiled and distributed online to 15 experts working in Italian Fabry reference centres, and their responses collected and analysed. Statements on: 1) Diagnosis; 2) Starting ERT; 3) Management of ERT infusion and adverse reactions; and 4) Follow-up/monitoring of response to therapy and disease progression, were included. Responses without consensus discussed with an enlarged Delphi panel of 50 clinicians with the aim of achieving consensus.

Results: All 15 experts responded to the survey. After plenary discussion among the enlarged Delphi panel, consensus was reached on most statements. Key points were the use of a target organ biopsy to show Gb3 deposits in symptomatic women with no identified pathologic mutation and negative molecular analysis, the need for ERT in symptomatic women and in all patients with persistent signs and symptoms with or without organ damage. It was agreed to assess vital signs before ERT administration and use a 0.2 μL filter on infusion to reduce the risk of adverse reactions. It was agreed that serum should be drawn before starting the first infusion, to be stored and analysed for antibodies if an adverse reaction occurs, and that pre-medication should be given in patients with history of infusion reactions. Holter electrocardiographic monitoring, cardiac and brain magnetic resonance imaging, renal parameters, and abdominal ultrasound were considered important for the assessment of disease progression and treatment response.

Conclusions: In the absence of abundant clinical evidence due to the rarity of this condition, the results of this Delphi panel provide welcome guidance to healthcare providers on best practice in the management of patients with Fabry disease. Findings from this survey and Delphi panel indicated a need for more guidance on some aspects of diagnosis and treatment.

Keywords: Fabry disease, diagnosis, treatment, management

Background

Despite the growing interest and an increasing amount of published literature [1] and clinical data on Anderson Fabry disease – an X-linked progressive multi-organ, metabolic lysosomal storage disorder caused by deficiency in the lysosomal enzyme alpha-galactosidase A leading to accumulation of glycosphingolipids (mainly globotriaosylceramide or Gb3) throughout the body – there are still uncertainties in terms of disease management [2]. In addition, goals of treatment are not clearly defined, due in part to the heterogeneity of the disease [3]. Moreover, Fabry patients can be treated in a range of settings from specialist reference centres to non-specialist therapeutic units, therefore a clear guidance on Fabry Disease is welcome. Current treatments consist of enzyme replacement therapy (ERT) and palliative treatments [4-11]. Two ERT drugs are available for the treatment of the disease.

Objectives

The objective of this paper is to report the results generated by a Delphi consensus panel on some unanswered question related to clinical and therapeutic aspects of Fabry disease – particularly with respect to agalsidase alfa.

Method

The Delphi process

The rationale for using the Delphi method to achieve consensus has been previously published [12, 13]: the Delphi method is a way of collecting opinions from experts – "a Delphi panel" – and is widely applied in various fields, including healthcare, to obtain consensus or to provide recommendations on a well-defined and specified topic. Although often referred to as a 'panel', the experts provide their opinions freely, individually and anonymously and this method

provides a quick and economic way to contact a large group of experts.

PHASE 1 – premeeting

A survey, designed to gauge the level of consensus among a group of expert health professionals from well-known centres of excellence in the diagnosis and management of Fabry disease, was created by two experts (DC and RP) and distributed online to participating clinicians; their responses were then collected anonymously and analysed prior to the enlarged meeting.

Participants voted using a 5-point scale to indicate their level of agreement on each statement (1 = absolutely disagree, 2 = disagree, 3 = agree, 4 = more than agree, 5 = absolutely agree). Consensus was reached when the sum of items 1 + 2 or 3 + 4 + 5 exceeded 66%.

The coordinators evaluated the responses and gathered those for which there was no consensus.

PHASE II – Delphi panel

Experts from a range of fields participated in the face-to-face Delphi panel discussions, ensuring a multidisciplinary approach, and allowing opinions and views from different perspectives to be expressed. Participants' specialty, the number of follow-up patients they have with Fabry disease, and the proportion of infused patients, were recorded.

Statements were divided into 4 main areas: 1) Diagnosis; 2) Starting ERT; 3) Management of ERT infusion and adverse reactions with agalsidase alfa; and 4) Tests to evaluate the response to therapy and disease progression (follow-up of patients with Fabry disease). Statements without consensus were selected for discussion in the Delphi plenary session. After discussion, and modification of the statements if required, participants reflected on the comments raised in the discussion and voted again using the same 5-point scale.

Results

Participants

The 15 experts surveyed were from the different specialties involved in the management of patients with Fabry disease: nephrology, cardiology, neurology, paediatrics and dermatology. Their expertise in dealing with Fabry disease was based on experience gained on diagnosing and treating more than three patients.

Overall consensus

Four statements for which consensus were not achieved in the survey were selected for discussion in the Delphi plenary session of 50 experts. After discussion, and in some cases, revision of the statement, second votes were taken on the four statements. After the second vote, consensus was reached on one statement; therefore, consensus (>66% either positive or negative) was reached on all but three statements according to the pre-defined criteria (**Figure 1**).

Diagnosis of Fabry disease

There was a negative consensus on four of five statements relating to diagnosis (**Figure 2**). None of the following were regarded as essential for diagnosis: presence of angiokeratoma, abdominal ultrasound, renal alteration on echocardiography, and target-organ biopsy showing Gb3 deposits in men.

Regarding the requirement for detecting Gb3 deposits on target-organ biopsy for diagnosis in women, the phrase “when they present with signs and symptoms of disease” and “the molecular analysis is negative” was added following discussion. Positive consensus was then achieved. In addition, during discussion, it also emerged that there was agreement on detecting Gb3 deposits in plasma and urine as a less invasive investigation in other patients.

Starting ERT in patients with Fabry disease

Positive consensus was obtained on the initiation of ERT in all symptomatic women and in men with persistent signs and symptoms (a new statement added after discussion). Statements regarding treating all patients with ERT on diagnosis, and use of ERT only if there is organ damage, both achieved negative consensus (**Figure 3**) [one after revision], and the statement on treating all males even if asymptomatic, did not achieve consensus even after discussion (**Figure 1**).

Management of ERT and adverse reactions in Fabry disease

Consensus was achieved on all statements (**Figure 4**), two on the second vote. Participants agreed that vital signs – heart rate, blood pressure and body temperature, as well as respiratory rate and oxygen saturation ($SATO_2$) – should be measured before and after ERT infusion.

Positive consensus was achieved after discussion with the immunologist to highlight the importance of using an integral 0.2 μL IV filter with the agalsidase alfa infusion line to eliminate aggregates, known to be a potential cause of infusion reactions.

In the event of a mild-to moderate adverse reaction, participants agreed that the infusion should be discontinued and restarted at a slower rate once the symptoms had regressed. However, with severe adverse reactions all participants agreed that the infusion should be stopped immediately and not restarted in the same day.

The need for determination of antibodies before starting treatment and in the case of an infusion reaction also achieved positive consensus.

Follow-up in Fabry disease

Ten statements on assessment to be performed at baseline and follow-up achieved positive consensus: Holter electrocardiography (ECG), cardiac magnetic resonance imaging (cMRI), microalbuminuria assessment, and abdominal echography or ultrasound (**Figure 5**). Two

statements regarding the use of Cystatin C assessment at baseline and follow-up did not achieve consensus even after discussion (**Figure 1**).

Management of pre-medication

A section on pre-medication was added and discussed. The results are shown in **Figure 6**. Participants disagreed that pre-medication should always be given before agalsidase alfa infusion. Positive consensus was achieved on the other two statements: pre-medication should only be given to patients with previous infusion reaction, and the protocol for pre-medication adverse reactions should be the same as for other protein preparations.

Discussion

In summary, all but four statements achieved consensus in the survey. After discussion of the contentious areas, lack of consensus remained for three statements relating to starting ERT in men regardless of symptoms, and assessment of Cystatin C at diagnosis or follow-up. There was negative consensus on four of five statements and positive consensus on one statement relating to diagnosis. Positive consensus was obtained on the initiation of ERT in all symptomatic women and in men with persistent signs and symptoms and negative consensus was achieved for statements regarding treating all patients with ERT on diagnosis, and use of ERT only if there is organ damage. Regarding management of ERT and adverse reactions in Fabry disease, consensus was achieved on all statements. In follow-up of patients with Fabry disease, 10 statements on assessments to be performed at baseline and follow-up achieved positive consensus. A section on pre-medication was added and discussed.

The following provides a brief description of the discussions held on the contentious issues.

Diagnosis

All participants agreed after discussion that angiokeratoma is not present in all patients,

especially at diagnosis. The presence of angiokeratoma correlates with age, rarely occurring during the first 10 years of age, even in males with the classical form of the disease. Its presence is dependent on the form of Fabry disease and correlates with severity [14, 15].

Although most participants thought that an abdominal ultrasound could be useful in patients with suspected renal involvement, but not essential to reach a diagnosis, from the clinical point of view, an abdominal ultrasound cannot lead to a differential diagnosis but does provide some additional renal information beyond proteinuria. It should be performed in all patients with suspected nephropathy regardless of its nature.

Cardiac involvement is common, but data from the literature show that not all patients have a 'renal' alteration on echocardiography; some patients do not show any cardiac involvement [16, 17].

In symptomatic women with no identified pathologic mutation and negative molecular analysis, the use of a target-organ biopsy to show Gb3 deposits could be indispensable. In patients with positive molecular analysis, but negative signs and symptoms of illness, the less invasive investigation – detection of Gb3 in plasma and urine – can be used.

Starting ERT

No consensus was achieved for the statement "ERT should be started always in males, even if asymptomatic"; there are very mild mutations which do not cause any signs and symptoms, not even in males until they are elderly. Paediatricians make their choice of whether to start ERT based on the mutation, signs and symptoms and family history.

Following discussion, the statement regarding starting ERT only if the parameters suggesting organ damage are altered, was rephrased as follows "ERT should be started only when the disease involves heart, kidney and brain". The misleading part of the sentence was 'organ function parameters' since organ function can involve not only the heart and the kidney, but also

hearing impairment, gastrointestinal disorders, quality of life, etc. for which there are no numerically measurable parameters. In this revised format, the statement achieved negative consensus. However, in view of this discussion, another statement "ERT should be started when the patient has persistent signs and symptoms with or without organ damage" was added and achieved positive consensus.

Management of ERT and adverse reactions

In clinical practice, in addition to standard assessment of BP, HR, and body temperature, most clinicians measured respiratory rate and oxygen saturation even in patients with normal respiratory function.

There was some discussion regarding the 79% agreement on the statement about use of an infusion line with integral 0.2 μL filter for the administration of agalsidase alfa to reduce particulate matter and microaggregates. The immunologists considered this to be of vital importance and were surprised that 21% of the clinicians did not agree with this statement, given that most infusion reactions are not related to antibody-mediated reactions, but are related predominantly to the presence of aggregates in solution. Infusion procedures should be standardized for all protein derivatives in order to reduce the risk of adverse events which may be related to the presence of aggregates and complexes and The Royal College of Nursing Standards for Infusion Therapy state that in-line filtration should be used [18]. In addition to these clinical considerations, the agalsidase alfa summary of product characteristics recommends the use of a filter [19]; therefore, there could be medical-legal issues if it is not used. After discussion, 100% positive consensus was achieved on the second vote.

For one statement, "I think that antibodies should be determined before starting the treatment", no consensus was achieved at the first vote. The importance of setting a baseline value, by which subsequent changes can be compared, was emphasized. From a practical point of view,

serum can be taken and stored safely, as antibodies are stable over time, and then analysed if an adverse reaction occurs. After discussion, 95% positive consensus was achieved.

Pre-medication

Additional discussion on the specific use of pre-medication led to the addition of three statements relating to pre-medication, and positive consensus was achieved on the use of pre-medication only in patients with previous infusion reactions, and use of a standard protocol used for other protein preparations in the advent of an adverse reaction with pre-medication.

Follow-up

Assessments related to cardiac involvement are particularly useful as abnormalities can be detected at an early stage before hypertrophy and fibrosis have developed [20]. Holter ECG monitoring is easy to do and it is particularly important in adolescents because clinical trials show that heart rate variability is altered in the early stage of disease before onset of hypertrophic cardiomyopathy [21].

cMRI is also a useful tool for assessing early cardiac involvement at diagnosis because it provides additional information to the Holter ECG, such as assessment of cardiac mass and detection of left ventricular hypertrophy [22], and can detect the patterns of late gadolinium enhancement specific to Fabry disease [22, 23] and has the advantage of being non-invasive. cMRI is equally important at follow-up and is especially useful for detecting fibrosis [24]. It provides information about disease progression and response to ERT, as patients with severe late enhancement do not respond to ERT [25, 26]. The approach for using cMRI for diagnosis and follow-up is different in men and women due to gender differences in the patterns of cardiomyopathy seen [27]. A clinically important difference (progression or regression) can be detected by cMRI in as little as one year. Unfortunately, administration of gadolinium is contraindicated in patients with advanced renal insufficiency, so although very useful at follow-

up, it is not always possible in patients with advanced Fabry disease.

Regarding the assessment of microalbuminuria to detect nephropathy, in children and in all patients who do not provide appropriate 24-hour urine samples, an accepted method is to take the mean of microalbuminuria values from three consecutive morning urine samples – also measuring creatinine at the same time in order to assess the albumin-creatinine ratio; this method is used in patients with other diseases such as diabetes [28].

The use of brain MRI was discussed at length. It is considered to be useful at follow-up for monitoring of CNS damage, but not essential. A parenchymal MRI at follow-up is useful to determine if and when new ischemic lesions appear in order to associate them with clinical signs which may appear later on.

Lack of consensus

There was no consensus on three statements even after the plenary discussion and second voting. The statement "*Enzyme replacement therapy should always be started in males, even if asymptomatic*" reflects the previously discussed fact that mutations in males can cause a mild phenotype, only developing signs or symptoms at advanced age.

Although there was no consensus on the statements concerning assessment using Cystatin C at diagnosis (*"I think it is essential to assess Cystatin C at patient diagnosis")* and follow-up *("I think it is essential to assess Cystatin C at patient follow-up"*) due to variations in practice, it was pointed out that it could be a more appropriate test than glomerular filtration rate or creatinine serum level for monitoring the effect of treatment on renal function over time; therefore, clinicians should evaluate Cystatin C every 6 or 12 months [29-32]. Even if Cystatin C is tested only in specific high-risk patients (i.e. transplant patients), being an expensive examination, the importance of Cystatin C was emphasized and clinicians were urged to consider its use in a Fabry laboratory panel.

Conclusions

The Delphi method was used to obtain consensus on best practice on a range of topics related to diagnosis and treatment of patients with Fabry disease. The method is well known for its robustness in making highly valid and unbiased consensus findings. The clinical recommendations of the Delphi panel experts are summarized as follows:

1. Diagnosis must be suspected in individuals of both sexes who show suggestive symptoms of Fabry disease independently of the presence of angiokeratoma, or renal alterations on echocardiography. A biopsy of target organs to detect Gb3 deposits should be performed to reach diagnosis in symptomatic women with no identified pathologic mutation and negative molecular analysis. In other patients, the less invasive method of detecting Gb3 in plasma and urine can be used.
2. ERT must be started in all women and men with persistent signs and symptoms.
3. Always use an infusion line with integral 0.2 μL filter for administration of ERT.
4. A blood sample must be drawn and serum stored for baseline antibodies. It will be sent to the laboratory together with another sample taken only in the case of a reaction.
5. As far as agalsidase alfa is concerned, the use of premedication is recommended only if the patient has had previous reactions.
6. The 6- and 12-month follow up of the Fabry patient should include Holter monitoring, cMRI, microalbuminuria, and abdominal echography and brain MRI.

The results of this Delphi panel provide welcome guidance to healthcare providers on best practice in the management of patients with Fabry disease. The outcomes of this Delphi Panel shows some aspects of diagnosis and overall management of Fabry disease need to be improved and should be addressed further.

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List of abbreviations

ERT: enzyme replacement therapy

Gb3: globotriaosylceramide

Competing interests

D. C. and R. P. receives speaking fees from Shire. E. D. receives Delphi panel organization fees from Shire HGT. The Delphi working group have no conflict of interest. The consensus panel was supported by a grant from Shire . The article was prepared by a professional medical writer who was supported by Shire HGT.

Authors' contributions

D. C and R. P: analysis of survey responses, moderators of plenary discussions, reviews and approval of draft manuscript; E. D.: analysis of survey responses and organisation of Delphi panel; Delphi working group: participation in consensus meeting..

All authors read and approved the final manuscript.

Acknowledgements

Alphabetical listing of the members of the Delphi working group: Daniela Antuzzi; Bruno Bembi; Andrea Silvio Benso; Gianni Carraro; Cristina Chimenti; Loredana Colla; Maria Teresa Cuonzo; Goffredo Del Rosso; Marina Diomedi; Claudio Feliciani; Sandro Feriozzi; Anna Ficcadenti; Andrea Frustaci; Maria Gnarra; Margherita Maccarone; Michelangelo Mancuso; Andrea Matucci; Renzo Mignani ; Beatrice Musumeci; Patrizia Nencini; Stefania Piga; Antonio Pisani; Federica Re; Alessandro Salviati; Marco Spada; Alessandra Vultaggio; Elisabetta Zachara; Maria Luisa Zedde; Pier Giorgio Zoli; We thank Mary Hines who provided medical writing services on behalf of Shire.

Figure legends

Figure 1 Statements on Fabry disease for which there was no consensus. The proportions of respondents responding absolutely disagree/disagree and agree/more than agree/absolutely agree shown as a percentage. Absolute numbers of votes are also shown on the bars.

Figure 2 Responses to statements on the diagnosis of patients with Fabry disease. The proportions of respondents responding absolutely disagree/disagree and agree/more than agree/absolutely agree shown as a percentage. Absolute numbers of votes are also shown on the bars.

Figure 3 Responses to statements on starting enzyme replacement therapy (ERT) in patients with Fabry disease. The proportions of respondents responding absolutely disagree/disagree and agree/more than agree/absolutely agree shown as a percentage. Absolute numbers of votes are also shown on the bars.

Figure 4 Responses to statements on the management of enzyme replacement. therapy (ERT) infusion and adverse reactions in patients with Fabry disease. The proportions of respondents responding absolutely disagree/disagree and agree/more than agree/absolutely agree shown as a percentage. Absolute numbers of votes are also shown on the bars.

Figure 5 Responses to statements on the follow-up of patients with Fabry disease. The proportions of respondents responding absolutely disagree/disagree and agree/more than agree/absolutely agree shown as a percentage. Absolute numbers of votes are also shown on the bars.

Figure 6 Responses to added statements on the management of pre-medication in patients with Fabry disease. The proportions of respondents responding absolutely disagree/disagree and agree/more than agree/absolutely agree shown as a percentage. Absolute numbers of votes are also shown on the bars.

Table

Table 1 Clinical recommendations

Diagnosis	In women presenting with signs and symptoms of disease, no pathologic mutation and negative molecular analysis, a Gb3 biopsy is essential. In other patients, a less invasive option of detecting Gb3 in plasma and urine can be useful.
Starting ERT	Enzyme replacement therapy should be started when the patient has persistent signs and symptoms with or without organ damage
Management of ERT agalsidase alfa infusion and adverse reactions	It is important to assess vital signs (BP, HR, respiratory rate, $SATO_2$) and temperature before the administration of ERT
	Use of an infusion line with integral filter (for 0.2 μL intravenous infusion) is recommended
	Collect and store sample before the first infusion is started, so that antibody values can be evaluates if any adverse event occurs
	Premedication should only be given to patients with previous infusion reaction with therapeutic approach similar to the one used for other protein infusion

Pre-medication	Before agalsidase alfa infusion, pre-medication should only be given in patients who have previously had an infusion reaction In case of adverse reactions with the pre-medication, the same protocol as for the other protein preparations should be followed
Follow-up	At baseline and 6/12 months' follow-up the following are essential: • Holter monitoring to detect changes in heart rate variability • Cardiac magnetic resonance imaging • Microalbuminuria • Abdominal echography • Brain magnetic resonance imaging There was NO consensus on assessment using Cystatin C