Surveillance report – Idiopathic pulmonary fibrosis (2013) NICE guideline CG163

September 2015

Surveillance decision

We will not update the guideline at this time.

Reason for the decision

We found 13 new studies relevant to the guideline through the surveillance process.

This included new evidence on pulmonary rehabilitation that supports current recommendations. We also identified a study of N-acetylcysteine that suggests that it is not effective in idiopathic pulmonary fibrosis. We asked topic experts whether this new evidence would affect current recommendations on N-acetylcysteine. Generally, the topic experts thought that an update was not needed.

We also found new evidence on ambulatory oxygen and other drug treatments. None of the new evidence was thought to have an effect on current recommendations.

We did not find any new evidence on awareness of clinical features, diagnosis, prognosis, information and support, lung transplantation, ventilation, or review and follow-up.

None of the new evidence considered in surveillance of this guideline was thought to have an effect on current recommendations.

See ‘how we made the decision’ for further information.

Commentary on selected new evidence

With advice from topic experts we selected 2 studies for further commentary.

Management – pharmacological interventions (N-acetylcysteine)

We selected the PANTHER-IPF trial for a full commentary because it strengthens the evidence base on N-acetylcysteine.

What the guideline recommends

NICE CG163 states 'there is no conclusive evidence to support the use of any drugs to increase the survival of people with idiopathic pulmonary fibrosis.'

It says: 'Advise the person that oral N-acetylcysteine is used for managing idiopathic pulmonary fibrosis, but its benefits are uncertain.' When this surveillance report was published, N-acetylcysteine did not have a UK marketing authorisation for idiopathic pulmonary fibrosis.

Methods

The Idiopathic Pulmonary Fibrosis Clinical Research Network (2014) reported results of the PANTHER-IPF trial. This was designed as a 3-arm trial in which participants were randomly assigned to prednisone plus azathioprine plus N-acetylcysteine or to N-acetylcysteine alone or to placebo. However, the 3-drug group was stopped because of safety concerns and the trial continued as a 2-arm study of N-acetylcysteine (600 mg/day) compared with placebo (n=264).

The trial included people aged 35–85 years (mean 67 years) with idiopathic pulmonary fibrosis and mild-to-moderate impairment in lung function. This was defined as forced vital capacity (FVC) of 50% or more of the predicted value and carbon monoxide diffusion capacity of 30% or more of the predicted value. The primary outcome was change in FVC over 60 weeks.

Results

At baseline, mean FVC was 2.9 litres in both groups (about 73% of the predicted value) and mean carbon monoxide diffusing capacity was 45% of the predicted value. At 60 weeks FVC had reduced by 0.18 litres in the N-acetylcysteine group and by 0.19 litres in the placebo group. This was not significant (mean difference 0.01 litres, 95% CI −0.06 to 0.09, p=0.77).

No significant differences were seen for the secondary outcomes of carbon monoxide diffusing capacity, distance on 6-minute walk test, score on the St George's Respiratory Questionnaire, or the University of California and San Diego Shortness of Breath Questionnaire. For most outcomes, such as FVC, the lack of statistical significance was driven by very small differences between groups.

Significant differences in some serious adverse events were seen. Cardiac disorders occurred in 6.8% of people in the N-acetylcysteine group and in 1.5% of the placebo group (p=0.03). The authors did not specify the type of cardiac disorders that were deemed to be a serious adverse event. No serious gastric disorders were recorded in the N‑acetylcysteine group, but affected 4.6% of participants in the placebo group.

Strengths and limitations

Strengths

A strength of this study is that it looked at a larger group of people than the studies assessed when developing the guideline.

Limitations

A limitation is that the authors conducted sub-analyses of data collected both before the clinical alert that stopped the 3-drug arm of the trial and then again afterwards. Scores before and after the clinical alert were different for some outcomes, particularly subjective measures of quality of life. The authors did not explain these differences, or why they split the data in this way.

If participants in the 2 groups that finished the study were aware of the problems with the study, this could have biased the scores after the clinical alert. In addition, if the clinical alert resulted in breaking of blinding, it could have biased the between-group analysis afterwards.

Impact on guideline

NICE CG163 does not make a recommendation about offering N-acetylcysteine to people with idiopathic pulmonary fibrosis. N-acetylcysteine does not have a marketing authorisation in the UK for idiopathic pulmonary fibrosis, but it is widely available as a dietary supplement. Patients may learn of and ask their clinicians about using N-acetylcysteine.

The guideline notes that doctors should advise people that although N-acetylcysteine is used for managing idiopathic pulmonary fibrosis, its benefits are uncertain. The new evidence suggests that N-acetylcysteine does not benefit people with idiopathic pulmonary fibrosis.

The studies of N-acetylcysteine that informed the guideline included a maximum of 90 people, whereas the PANTHER-IPF trial included almost 3 times as many people. This strengthens the evidence base on N-acetylcysteine in idiopathic pulmonary fibrosis.

We asked topic experts whether they thought that this new evidence had an effect on the current recommendation. Because the guideline already acknowledges uncertainty about the benefits of this drug, and no new safety concerns have been raised about its use by the MHRA, there is no urgent need to review this recommendation. This area will be examined again at the next surveillance review of the guideline.

Management – pulmonary rehabilitation

We selected a Cochrane review by Dowman et al. (2014) for full commentary because it supports existing recommendations on pulmonary rehabilitation.

What the guideline recommends

NICE CG163 recommends assessing people with idiopathic pulmonary fibrosis for pulmonary rehabilitation at the time of diagnosis. Assessment may include a 6-minute walk test (distance walked and oxygen saturation measured by pulse oximetry) and a quality-of-life assessment. The assessment for pulmonary rehabilitation should be repeated at 6-month or 12-month intervals. If appropriate after each assessment, pulmonary rehabilitation should be offered including exercise and educational components tailored to the needs of people with idiopathic pulmonary fibrosis in general.

Methods

Dowman et al. (2014) conducted a Cochrane review of 9 randomised controlled trials of pulmonary rehabilitation for interstitial lung diseases. Data from 4 of these studies were available to evaluate idiopathic pulmonary fibrosis separate from other interstitial lung diseases. All compared pulmonary rehabilitation with either a sham training control group or no pulmonary rehabilitation.

All evaluated interventions in idiopathic pulmonary fibrosis were outpatient programmes lasting 5–12 weeks that used a combination of aerobic exercise and resistance training. The primary outcome for meta-analysis was functional or maximum exercise capacity measured by change in maximum or peak oxygen uptake, maximum ventilation or heart rate, or increase in exercise tests such as distance walked.

Results

Compared with the control, pulmonary rehabilitation was associated with significant increases in:

- distance in the 6-minute walk test (mean difference [MD] 35.63 m, 95% confidence interval [CI] 16.02 to 55.23, p=0.0004; 4 studies, n=111)
- peak oxygen uptake (MD 1.46 ml/kg/min, 95% CI 0.54 to 2.39, p=0.002; 2 studies, n=58)

- maximum ventilation (MD 6.96 litre/min, 95% CI 0.87 to 13.07, p=0.025; 1 study, n=30)
- quality of life (MD 0.59, 95% CI 0.14 to 1.03, p=0.01; 3 studies, n=83).

It was also associated with significantly reduced dyspnoea (MD −0.68, 95% CI −1.12 to −0.25, p=0.002; 3 studies, n=90).

Strengths and limitations

Strengths

A strength of this systematic review is that it is a Cochrane review conducted according to a predefined protocol. In addition, the authors included studies published only as abstracts as well as studies published as full text articles, to increase the completeness of the evidence base. However, the authors could not get additional data for all of the abstracts and that may have affected the trial quality assessments.

The authors used GRADE (Grading of Recommendation, Assessment, Development and Evaluation) to assess the review outcomes. The outcome of the 6-minute walk test was rated as moderate quality, but all other outcomes were rated as low quality. Additionally, the results for the 6-minute walk test – a difference of 35.63 m favouring pulmonary rehabilitation – is within the range of minimally important difference of 24–45 m defined for this outcome in the guideline.

Limitations

However, the studies included in the review also had limitations. None of the included studies reported on adverse events during the intervention period. The small number of trials and participants meant that the results were fairly imprecise (shown by the wide confidence intervals).

The authors of the Cochrane review noted that studies in idiopathic pulmonary fibrosis would be likely to have a high drop-out rate because of the progressive nature of the condition. Only 1 study reported intention-to-treat analysis, 2 reported analysis excluding the people who dropped out, and 1 did not report whether drop-outs or losses to follow-up occurred. Excluding drop-

outs from analysis is likely to give a larger effect size than intention-to-treat analysis and thus bias the results in favour of the intervention.

Impact on guideline

The new evidence suggests that pulmonary rehabilitation programmes increase functional and exercise capacity and quality of life for people with idiopathic pulmonary fibrosis.

The effect sizes for the outcomes of 6-minute walk test, dyspnoea, and quality of life were slightly higher than those found when developing the guideline. This potentially strengthens the evidence in favour of the existing recommendation to offer pulmonary rehabilitation if assessment shows it is appropriate.

How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 2 years after the publication of Idiopathic pulmonary fibrosis (2013) NICE guideline CG163.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual'.

New evidence

We found 11 new studies in a search for randomised controlled trials published between 1 November 2012 and 13 February 2015. We also considered 2 additional studies identified by members of the Guideline Committee who originally worked on this guideline. From all sources, 13 studies were considered to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review.

See appendix A: decision matrix for summaries and references for all new evidence considered.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline.

Views of stakeholders

Stakeholders are consulted only if we decide not to update the guideline following checks at 4 and 8 years after publication. Because this was a 2-year surveillance review, and the decision was not to update, we did not consult on the decision.

See ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual' for more details on our consultation processes.

Date of next surveillance

Our next surveillance to decide whether the guideline should be updated is scheduled for 2017.

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