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[Intervention Review]

Disease modifying anti-rheumatic drugs in people with cystic fibrosis-related arthritis

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ABSTRACT

Background

Arthritis remains a relatively infrequent complication of cystic fibrosis, but is a cause of significant morbidity when it does occur. Two distinct types of arthritis are described in cystic fibrosis: cystic fibrosis-related arthropathy and hypertrophic osteoarthropathy. Management of arthritis in people with cystic fibrosis is uncertain and complex because of the underlying disease and its treatment.

Objectives

To review the effectiveness and safety of disease-modifying anti-rheumatic drugs for the management of arthritis related to cystic fibrosis in adults and children.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Cystic Fibrosis Trials Register which comprises references identified from comprehensive electronic database handsearches of relevant journal and abstract books of conference proceedings.

Date of most recent search: 10 July 2012.

Selection criteria

Randomised controlled trials which compared the efficacy and safety of disease-modifying anti-rheumatic drugs (e.g. methotrexate, gold, sulfasalazine, penicillamine, leflunomide, hydroxychloroquine and newer agents such as biologic disease modifying agents and monoclonal antibodies) with each other, with no treatment or with placebo for cystic fibrosis-related arthropathy or hypertrophic osteoarthropathy.

Data collection and analysis

No relevant studies were identified.

Main results

No studies were included in this review.

Authors' conclusions

Although it is generally recognised that cystic fibrosis-related arthritis can be episodic and resolve spontaneously, treatment with analgesics and anti-inflammatory agents may be needed. But when episodic symptoms progress to persistent disease, disease-modifying

anti-rheumatic drugs may be needed to limit the course of the disease. It is disappointing that no randomised controlled trials to rigorously evaluate these drugs could be found. This systematic review has identified the need for a well-designed adequately powered randomised controlled trial to assess the efficacy and safety of disease-modifying anti-rheumatic drugs for the management of cystic fibrosis-related arthropathy and hypertrophic osteoarthropathy in adults and children with cystic fibrosis. However, given the infrequency of cystic fibrosis-related arthritis and the range of symptoms and severity, randomised controlled trials may not be feasible and well-designed non-randomised observational studies may be more appropriate. Studies should also better define the two conditions.

PLAIN LANGUAGE SUMMARY

The use of drugs to slow or stop progression of arthritis related to cystic fibrosis

Arthritis is not a common complication of cystic fibrosis, but it can cause major problems when it does occur. There are two distinct types of arthritis in cystic fibrosis: cystic fibrosis-related arthropathy and hypertrophic pulmonary osteoarthropathy. The best treatment for these types of arthritis is not clear because of cystic fibrosis and its intense treatment. Some drugs can treat the symptoms of arthritis by reducing inflammation of the joints and relieving pain, but only disease modifying anti-rheumatic drugs can stop or slow progression of the disease. We planned to report evidence from clinical trials which compared different disease-modifying drugs compared with placebo (or dummy treatment), with each other or with no treatment. However, we were disappointed that we could not find any completed randomised controlled trials of these treatments or any evidence from non-randomised controlled trials. We suggest that there should be a randomised controlled trial to look at the effects and the safety of using disease modifying anti-rheumatic drugs to slow or stop the progression of arthritis in people with cystic fibrosis.

BACKGROUND

Description of the condition

Arthritis in cystic fibrosis (CF) was first described by Ansell and Newman in 1979 when they reported five children with recurrent episodes of joint pain swelling and stiffness (Newman 1979). However, there has been little recent research in this area. Arthritis remains a relatively infrequent complication of CF but is a cause of significant morbidity when it does occur (Botton 2003). Two distinct types of arthritis are described in CF: cystic fibrosis-related arthropathy (CFA) and hypertrophic pulmonary osteoarthropathy (HPO).

The most common form of joint disease in CF is CFA (Johnson 1994), but relatively few cases have been described. Two literature reviews reported 71 (Turner 1997) and 72 (Botton 2003) individual cases of CFA in adults and children. The prevalence of CFA is uncertain but it has been estimated as between 2% and 8.5% (Botton 2003; Johnson 1994). The mean age at onset has been reported as 13.6 years (Turner 1997) and 17 years (Merkel 1999); however, Merkel stated that this may have been overestimated if the arthritis had been present but undiagnosed for some years. As people with CF are living longer, the prevalence of CFA may be increasing (Merkel 1999); for example in France, life expectancy at birth has increased from 30.4 years for people born between 1994 and 1996 to 39.1 years for those born between 2001 and 2003 (Bellis 2007). There is no formal definition of CFA, but it consists of distinct symptoms (Merkel 1999; Turner 1997) such as recurrent episodes of joint pain, swelling, tenderness and limitation of movement which may be disabling (Johnson 1994; Merkel 1999; Rush 1986; Turner 1997). Joint pains develop over approximately 12 to 24 hours and episodes last less than one week (Turner 1997). Symptoms can disappear completely between attacks (Turner 1997). One or more joints may be affected and involvement is often asymmetric. There may also be fever and skin manifestations. Radiographs tend to be normal (Johnson 1994; Turner 1997); only one study reported abnormalities on X-rays of affected joints (Rush 1986). In general, there are no differences in lung function, respiratory pathogens, gastrointestinal symptoms or treatment between people with CF with and without arthritis, and exacerbations of joint symptoms are generally not associated with exacerbations of pulmonary disease (Johnson 1994; Turner 1997). It is possible that CFA may become persistent and disabling (Johnson 1994; Merkel 1999; Turner 1997). The pathogenesis and aetiology of CFA are unclear. Even when it develops into persistent disease, CFA appears to be clinically distinct from most recognised forms of joint disease and it may not fulfil the criteria for rheumatoid arthritis (Dixey 1988; Johnson 1994). There could be a genetic predisposition for CFA, but no recent genotyping has been done and no human leukocyte antigen (HLA) association with CFA has been reported in earlier work (Johnson 1994; Merkel 1999). It is possible that CFA could be another phenotypic expression of the underlying defect in CF (Merkel 1999). In addition, CFA may be a reactive arthritis (Johnson 1994; Merkel 1999; Rush 1986; Turner 1997). Doyen reported on three people who presented with a *Staphylococcus aureus* infection before rheumatoid arthritis occurred which was consistent with the American College of Rheumatology criteria (Doyen 2005). It has been reported that CFA has developed after treatment with fluoroquinolone antibiotics, but results from studies examining this association are equivocal (Turner 1997).

In people with CF, HPO is less common than CFA with a prevalence of between 2% and 7% (Botton 2003; Braude 1984; Johnson 1994). It is defined as the occurrence of periosteal proliferation (new bone formation) of long bones in association with digital clubbing (Merkel 1999; Turner 1997). It usually starts as a dull bone pain or episodic joint pain (Turner 1997) and is usually seen in people with CF with more severe lung disease; it worsens during intercurrent pulmonary infection and often presents at this time (Johnson 1994; Merkel 1999). People with HPO are more likely to be colonised with *Pseudomonas aeruginosa* and have a worse prognosis than people without HPO (Johnson 1994; Rush 1986). The median age onset for HPO in CF is older than for CFA, at around 20 years of age (Botton 2003; Johnson 1994; Turner 1997). As for CFA, there has been little recent research into this condition and the causes of HPO are unknown (Khan 2008).

Arthritis in CF can also consist of other conditions such as co-existent rheumatoid arthritis. Doyen reported on three people with CF with rheumatoid arthritis (Doyen 2005). There was a strong association between respiratory status and rheumatoid activity in these people. However, rheumatoid arthritis and the other connective tissue disorders are well-known to be independently associated with respiratory complications and this likely represents a distinct complicated group that are not necessarily representative of CF arthropathy in general. In addition, exposure to medications may also lead to arthritis and this has been described with quinolones, antibiotics and cimetidine (Johnson 1994; Merkel 1999; Turner 1997; Warren 1997).

The initial diagnosis depends on the clinical presentation (Turner 1997). Turner suggested that if a single joint is involved, a full blood count, measurement of acute phase reactants, radiograph of the affected joint and examination of synovial fluid should be performed (Turner 1997). In people with polyarticular involvement (affecting several joints), the extent of the disease should be assessed, its functional consequences measured and the joint(s) should be X-rayed. The distinction between CFA and HPO may be made radiographically. Clinicians should also look for an exacerbation of pulmonary infection, skin involvement (vasculitis rash or erythema nodosum) and consider other causes of inflammatory joint diseases along with the development of gout or pseudogout.

Description of the intervention

Management of arthritis in people with CF is uncertain and complex because of the underlying disease and its intense treatment. In rare cases where arthritis is linked to lung function, antibiotic treatment of the chest may help (Johnson 1994). It appears that HPO may respond to treatment of the chest with intravenous (IV) antibiotics and the resulting improved pulmonary status, rest and non-steroidal anti-inflammatory drugs (NSAIDs) help to relieve pain (Merkel 1999; Turner 1997). In general, acute attacks of CFA may resolve spontaneously and treatment is limited to alleviation of pain and stiffness, including bed rest and NSAIDs (Johnson 1994; Turner 1997). Oral prednisolone or intra-articular corticosteroids such as triamcinolone are sometimes needed. These interventions are the subject of a separate Cochrane Review which identified no controlled studies of analgesic and anti-inflammatory agents and further research is needed (Thornton 2012). When episodic symptoms progress to persistent disease, disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate or azathioprine may be tried or gold and hydroxychloroquine (Johnson 1994).

Why it is important to do this review

Although publications on the management of arthritis in CF are available, to date there has been no formal assessment of the available evidence on the use of DMARDs in this condition.

OBJECTIVES

To review the effectiveness and safety of DMARDs in CF-related arthritis in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

People of all ages with CF (diagnosed clinically and by sweat or genetic testing and including all degrees of disease severity) who have symptoms consistent with CF-related arthritis (for example joint pain, swelling, tenderness and limitation of movement) with clinical or radiological confirmation of the diagnosis. Studies of people with arthritis consisting of other conditions such as co-existent rheumatoid arthritis, sarcoidosis, psoriatic arthritis and drug reactions will be excluded.

Types of interventions

We plan to compare DMARDs (including methotrexate, gold, sulfasalazine, penicillamine, leflunomide, hydroxychloroquine and newer agents such as biologic disease modifying agents including monoclonal antibodies) with each other, with no treatment or with placebo for:

1. CFA;
2. HPO.

Types of outcome measures

Primary outcomes

1. Joint involvement
 - a. number of swollen joints
 - b. number of joints with limited range of movement
 - c. number of painful joints; pain assessed, for example, using visual analogue scales (VAS)
 - d. episodes of acute inflammatory joint involvement over a six-month period
2. Joint damage (i.e. localised destructive joint changes and deformity (to be assessed through radiology))
3. Physical function (to be assessed using instruments including disease-specific instruments (for example, Health Assessment Questionnaire (HAQ), Child Health Assessment Questionnaire (CHAQ), Child Health Questionnaire (CHQ) and Juvenile Arthritis Functional Status Index (JASI)), generic instruments and VAS; the Steinbrocker classification should also be considered)

Secondary outcomes

1. Quality of life (to be measured using various disease-specific and generic instruments including CHQ, Juvenile Arthritis Quality of Life Questionnaire (JAQQ), Pediatric Quality of Life (PedsQL)

and Quality of My Life Questionnaire (QoMLQ), Arthritis Impact Measurement Scale (AIMS), Nottingham Health Profile (NHP), Sickness Impact Profile (SIP), Short Form Health Survey 36 (SF36) and EQ-5D)

2. Psychosocial outcomes (to be assessed using disease-specific and generic instruments such as HAQ, SIP, Health Status Questionnaire, Coping Strategies Questionnaire, Daily Stress Inventory, Hassles Scale, State-Trait Anxiety Inventory, Arthritis Helplessness Index, Arthritis Self-Efficacy Scale)
3. Socio-economic outcomes (to be assessed as defined by the investigators, for example loss of schooling or unemployment because of illness)
4. Laboratory markers for chronic inflammation, for example c-reactive protein (CRP)
5. Adverse effects (for example, gastrointestinal effects)

Search methods for identification of studies

Electronic searches

We planned to identify relevant studies from the Group's Cystic Fibrosis Trials Register including the term 'arthritis'.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), quarterly searches of MEDLINE, a search of EMBASE to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the [Cystic Fibrosis and Genetic Disorders Group Module](#).

Date of most recent search of the CF Trials Register: 10 July 2012.

Searching other resources

We planned to check the reference lists of any studies identified for further relevant studies and will do so for future updates of this review.

Data collection and analysis

If any studies are identified in future updates of this review, we will apply the following methods.

Selection of studies

The authors (JT, SR) will independently apply the inclusion criteria to all potential studies. We will perform this without blinding and resolve any discrepancy through discussion.

Data extraction and management

Two authors (JT, SR) will independently extract the data (using a customised data extraction form) and resolve disagreements through discussion.

We plan to group outcome data into those measured at up to one month, over one month and up to three months, over three months and up to six months, over six months and up to one year and

annually thereafter. If outcome data are recorded at other time periods, we will consider examining these as well.

Assessment of risk of bias in included studies

We plan to independently assess the risk of bias of studies included in this review according to the criteria discussed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will assess the following criteria as having a low, unclear or high risk of bias.

Generation of the allocation sequence

We will assess methods used to assign participants to comparison groups in a study as follows:

low risk of bias - methods of randomisation include using a random number table, computer-generated lists or similar methods;
unclear risk of bias - if the study is described as randomised, but no description of the methods used to allocate participants to treatment group is provided;
high risk of bias - methods of randomisation include alternation; the use of case record numbers, dates of birth or day of the week, and any procedure that is entirely transparent before allocation.

Concealment of the allocation sequence

We will assess the process used to prevent foreknowledge of group assignment in a study as follows:

low risk of bias - if the allocation of participants involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacists or investigator, or sealed opaque envelopes;
unclear risk of bias - if the method used to conceal the allocation was not described;
high risk of bias - if the allocation sequence was known to or could be foreseen by the investigators who assigned participants or if the study was quasi-randomised.

Blinding (or masking)

We will assess the degree to which the group assignment (for example, whether a participant was part of the treatment or control arm) was accessible; if all people involved in a study are blinded to group assignment there will be a low risk of bias. The risk of bias will increase as the number of people (clinician, participant, outcome assessor) blinded decreases. We will assess the following groups for risk of bias:

1. clinician (person delivering treatment);
2. participants;
3. outcome assessors.

Intention-to-treat and follow up

An intention-to-treat (ITT) analysis is one in which all participants in a study are analysed according to the intervention to which they were allocated, whether they received it or not. We plan to report whether the investigators performed an ITT analysis and if they didn't, we plan to report the analysis that was performed.

We plan to assess whether the numbers and reasons for dropouts and withdrawals in all intervention groups were described and balanced across groups, or if it was specified that there were no dropouts or withdrawals; in this case there will be a low risk of bias. If it is apparent from the paper that there were withdrawals

but these are not discussed and reasons not given or they are not balanced across groups, then we will regard the study as having a high risk of bias.

Sample size calculation

We plan to report on whether the investigators performed a sample-size calculation, for which outcome and the method used.

Measures of treatment effect

For binary outcome measures, we aim to calculate a pooled estimate of treatment effect for each outcome across studies using risk ratio where appropriate.

For continuous outcomes, we plan to record either mean relative change from baseline for each group or mean post-treatment or intervention values and standard deviation. If standard errors are reported, and where possible, these will be converted to standard deviations. We will calculate a pooled estimate of treatment effect by calculating the mean difference.

If we find any count data, we will decide whether to treat this as dichotomous, continuous, time-to-an-event or as a rate. Although we accept that it is preferable to decide how count data will be analysed in advance, we think our choice will be determined by the format of the available data and thus can not be decided until most studies have been reviewed. We planned to analyse such data as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Where studies measure data longitudinally, we plan to base our analysis on the final time-point results which is a common method used in Cochrane Reviews (Jones 2005). We accept that this analysis would treat the data as independent, although in reality they are not. However, methods are not yet available to carry out a meta-analysis of aggregate longitudinal data, unless we are able to obtain any individual patient data (IPD).

Unit of analysis issues

When conducting a meta-analysis combining results from cross-over studies we plan to use the methods recommended by Elbourne (Elbourne 2002). However, if only limited data are available, we will only be able to either use the first-arm data only or to treat the cross-over studies as if they are parallel studies. Elbourne states that this approach will produce conservative results as it does not take into account within-patient correlation (Elbourne 2002). Also each participant will appear in both the treatment and control group, so the two groups will not be independent.

We do not plan to combine data from parallel trials with data from cross-over trials; these will be analysed separately.

Dealing with missing data

In order to allow an intention-to-treat analysis, we plan to seek data on the number of participants with each outcome event, by allocated treated group, irrespective of adherence and whether or not the individual was later thought to be ineligible or otherwise excluded from treatment or follow-up.

Assessment of heterogeneity

We plan to assess the degree of heterogeneity between studies using the I^2 statistic (Higgins 2003). This measure describes the percentage of total variation across studies that are caused by heterogeneity rather than by chance (Higgins 2003). The values of I^2 lie between 0% and 100%, and a simplified categorization of heterogeneity that we plan to use is of low (I^2 value of 25%), moderate (I^2 value of 50%), and high (I^2 value of 75%) (Higgins 2003).

Assessment of reporting biases

We plan to report when measurements are taken by the primary investigators during the study, what measurements are reported within the published paper and what data we are reporting in the review.

We plan to assess whether our review is subject to publication bias by using a funnel plot. If asymmetry is detected, causes other than publication bias will be explored.

Data synthesis

If we find significant heterogeneity, we will compute pooled estimates of the treatment effect for each outcome using a random-effects model. If no significant heterogeneity is identified, we plan to compute pooled estimates of the treatment effect for each outcome under a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

If we find at least moderate heterogeneity (over 50%), we will investigate the possible causes further by performing subgroup analyses based on the type of treatment for example, participants on methotrexate or other immunosuppressive or immunomodulatory treatment and those without such treatment.

Sensitivity analysis

We will also test the robustness of our results through a sensitivity analysis on the basis of the risk of bias of the included studies, for example, including and excluding studies with a high risk of bias for allocation concealment.

RESULTS

Description of studies

No studies were found that were eligible for inclusion in the review.

Risk of bias in included studies

No studies were found that were eligible for inclusion in the review.

Effects of interventions

No studies were found that were eligible for inclusion in the review.

DISCUSSION

Cystic fibrosis-related arthropathy (CFA) and hypertrophic pulmonary osteoarthropathy (HPO) are relatively infrequent complications of cystic fibrosis (CF) and few cases have been described in the literature (Botton 2003; Turner 1997). It is disappointing that there are no randomised controlled trials to rigorously evaluate the efficacy and safety of disease modifying

anti-rheumatic drugs (DMARDs) for limiting the progression of arthritis in people with CF-related arthritis. Following this, the authors further investigated whether any other evidence was available for the use of these agents, but found no quasi-randomised or non-randomised trials. Three publications described case reports or series of five individuals with severe arthritis related to CF who were managed with suphasalazine, sodium aurothiomalate, methotrexate or leflunomide (Benjamin 1990; Doyen 2005; Sagransky 1980). There was only limited success of these treatments with further deterioration of symptoms or poor tolerance which led to the discontinuation of the drugs.

AUTHORS' CONCLUSIONS

Implications for practice

No conclusions can be made about the efficacy and safety of DMARDs for the management of arthritis related to CF in adults and children. Clinicians must balance potential benefit against the possible risk of complications in each case.

Implications for research

This systematic review has identified the need for a multi-centred trial to assess the efficacy and safety of disease modifying anti-rheumatic drugs for the management of arthritis related to CF in adults and children. The trial should take into account both subgroups of arthritis (CFA and HPO) and the state of pulmonary and hepatic involvement. Although the management of early stages, where disease may be self-limiting, can be achieved with simple anti-inflammatory and analgesic agents, the management of persistent and disabling disease is of more concern for future research. It is important to determine whether DMARDs should be started when treatment with anti-inflammatory and analgesic agents is found to be inadequate or whether they should be instituted at earlier stages of disease to prevent progressive damage as is recommended in the management of arthritis in people who do not have CF (Luqmani 2006). Given the infrequency of arthritis related to CF and the range of symptoms and severity, RCTs may not be feasible to study such long-term management. Well-designed non-randomised observational studies may be more appropriate. As recommended in our previous review of anti-inflammatory and analgesic agents, further research is also needed to better characterise CFA and HPO (Thornton 2012).

We suggest the following:

1. studies should be undertaken to better define CFA and HPO;
2. that researchers should use national databases to determine the extent of CFA and HPO;
3. studies should evaluate the disease stage at which treatment with DMARDs should be initiated;
4. the short-term efficacy and safety of different DAMRDs should be assessed; the choice of the most appropriate agent(s) for use in CFA and HPO should be evaluated.
5. the optimum duration of treatment with DMARDs should be evaluated; long-term efficacy and safety should be evaluated if appropriate.

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Nikki Jahnke and Tracey Remington, Cochrane Cystic Fibrosis & Genetic Disorders Review Group

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WHAT'S NEW

Date	Event	Description
29 June 2017	Amended	Contact details updated.
21 August 2012	Review declared as stable	This review will no longer be regularly updated. Searches will still be undertaken on a two-yearly basis by the Cochrane Cystic Fibrosis & Genetic Disorders Group. If, in future, relevant trials are identified, the review will be updated again.

HISTORY

Protocol first published: Issue 3, 2008

Review first published: Issue 1, 2009

Date	Event	Description
13 April 2015	Amended	Contact details updated.
11 July 2012	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any new references potentially eligible for inclusion in this review.
11 July 2012	New citation required but conclusions have not changed	Since no new information has been added to this review at this update, the conclusions have not changed.
22 May 2012	Amended	Contact details updated.
14 September 2010	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any new references potentially eligible for this review.
8 September 2010	Amended	Contact details updated.
12 August 2009	Amended	Contact details updated.
30 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Judith Thornton drafted the protocol and the review with comments and input from Satyapal Rangaraj. Judith Thornton is responsible for the updates and guarantor of the review.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Antirheumatic Agents [*therapeutic use]; Arthritis [*drug therapy] [etiology]; Cystic Fibrosis [*complications]

MeSH check words

Humans