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Saldanha IJ, Akinyede O, Robinson KA

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	5
METHODS	5
RESULTS	8
Figure 1.	9
DISCUSSION	10
AUTHORS' CONCLUSIONS	10
ACKNOWLEDGEMENTS	10
REFERENCES	12
CHARACTERISTICS OF STUDIES	14
APPENDICES	14
WHAT'S NEW	15
HISTORY	15
CONTRIBUTIONS OF AUTHORS	16
DECLARATIONS OF INTEREST	16
SOURCES OF SUPPORT	16
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	17
INDEX TERMS	17

[Intervention Review]

Immunosuppressive drug therapy for preventing rejection following lung transplantation in cystic fibrosis

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ABSTRACT

Background

For people with cystic fibrosis and advanced pulmonary damage, lung transplantation is an available and viable option. However, graft rejection is an important potential consequence after lung transplantation. Immunosuppressive therapy is needed to prevent episodes of graft rejection and thus subsequently reduce morbidity and mortality in this population. There are a number of classes of immunosuppressive drugs which act on different components of the immune system. There is considerable variability in the use of immunosuppressive agents after lung transplantation in cystic fibrosis. While much of the research in immunosuppressive drug therapy has focused on the general population of lung transplant recipients, little is known about the comparative effectiveness and safety of these agents in people with cystic fibrosis. This is the final update of a previously published review; no longer being updated due to a lack of research in the area.

Objectives

To assess the effects of individual drugs or combinations of drugs compared to placebo or other individual drugs or combinations of drugs in preventing rejection following lung transplantation in people with cystic fibrosis.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register and scanned references of the potentially eligible study. We also searched the www.clinicaltrials.gov registry and the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) to obtain information on unpublished and ongoing studies.

Date of latest search: 29 May 2018.

Selection criteria

Randomised and quasi-randomised studies.

Data collection and analysis

We independently assessed the studies identified from our searches for inclusion in the review. If we had found eligible studies to include in the review, we planned to independently extract data and assess the risk of bias. We planned to use GRADE to summarize our results through a summary of findings table for each comparison we could present in the review.

Main results

While five studies addressed the interventions of interest, we did not include them in the review because the investigators of the studies did not report any information specific to people with cystic fibrosis. Our attempts to obtain this information have not yet been successful.

Authors' conclusions

The lack of currently available evidence makes it impossible to draw conclusions about the comparative efficacy and safety of the various immunosuppressive drugs among people with cystic fibrosis after lung transplantation. A 2013 Cochrane Review comparing tacrolimus with cyclosporine in all lung transplant recipients (not restricted to those with cystic fibrosis) reported no significant difference in mortality and risk of acute rejection. However, tacrolimus use was associated with lower risk of broncholitis obliterans syndrome and arterial hypertension and higher risk of diabetes mellitus. It should be noted that this wider review contained only a small number of included studies ($n = 3$) with a high risk of bias. Additional randomised studies are required to provide evidence for the benefit and safety of the use of immunosuppressive therapy among people with cystic fibrosis after lung transplantation.

PLAIN LANGUAGE SUMMARY

Drugs to suppress the immune system after lung transplantation in people with cystic fibrosis

Review question

We reviewed evidence to find out the effects of individual drugs or combinations of drugs when they are given to prevent donor lungs being rejected following transplantation in people with cystic fibrosis. We only considered randomised studies (where it is decided at random which drug volunteers are given) comparing individual drugs or combinations of drugs to a placebo (dummy treatment with no active medicine) or to each other.

Background

Lung transplantation is an available and realistic treatment option for people with cystic fibrosis whose lungs are severely damaged. However, as a natural defence mechanism, the body recognises a transplanted lung as foreign and activates the immune system to reject it. This is known as graft rejection. To prevent this, drugs are needed to suppress the immune system after lung transplantation. There are several different types of such drugs that act by suppressing different components of the immune system. Much of the research on such drugs has focused on all people who have had a lung transplant and not specifically on those with cystic fibrosis. Currently, clinicians do not all agree on a common way of using anti-rejection drugs in people with cystic fibrosis after they have received a lung transplant.

Search date

The evidence is current to: 29 May 2018.

Study characteristics

Although we found five studies which looked at anti-rejection drugs, they included people with a number of chronic conditions and not just cystic fibrosis.

Key results

The studies we found reported results from all volunteers combined and we were not able to isolate the results that were specific to people with cystic fibrosis. We contacted the researchers who conducted these studies, but they have not sent us the specific results we need.

There is a review of drugs to suppress the immune systems of people who have had lung transplants (not restricted to those with cystic fibrosis) and this only included three studies which the review authors judged to have a high risk of bias. The review did not find that any one drug was better than another for reducing the chances of death or acute rejection; but one drug (tacrolimus) led to a lower risk of long-term rejection and high blood pressure, although there was a higher risk of diabetes.

Research is needed on the use of drugs that suppress the immune system in people with cystic fibrosis who have received a lung transplant. Due to the lack of research in this area, we do not plan to update this review again.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a common autosomal recessive multi-system disorder, occurring in approximately 1 in every 2500 live births (Ratjen 2003). In the USA, CF affects approximately 30,000 individuals and worldwide affects approximately 70,000 (Cystic Fibrosis Foundation 2013). It predominantly affects the lungs, pancreas, liver, and intestines. The main genetic defect is a mutation of the CF transmembrane conductance regulator (CFTR) gene, a gene responsible for a chloride channel that transports salt across the cell membrane (Rowe 2005). The abnormal salt transport, caused by the CF gene defect, results in viscous mucus. The increased viscosity of mucus makes it difficult for airway cilia to propel mucus out of the airways. Retention of this mucus leads to pulmonary colonisation of pathogenic bacteria. Recurrent colonisation and inflammation lead to chronic airway disease. Pulmonary disease accounts for most of the morbidity and mortality in people with CF (90% of fatalities) (Ramsey 1996).

For those with advanced pulmonary damage, lung transplantation is an available and realistic option (Jaramillo 2005). Although more people consider it, between 1990 and 2008 in the USA on average about 140 people with CF per year received lung transplants (Cystic Fibrosis Foundation 2011). Since May 2005 in the USA, eligible lung transplant candidates across indications are prioritised using the lung allocation score (LAS) system (Yusen 2010). The LAS system is based on a combination of medical urgency and expected post-transplant outcomes for individuals. In people aged 12 years and older, prioritisation is based on the LAS, in addition to ABO blood group and distance from the donor hospital. In those under 12 years of age, prioritisation is based on time on lung transplant waiting list, ABO compatibility, and distance from the donor hospital (Yusen 2010).

Cystic fibrosis was the indication for between 14% and 17% of all lung transplants, both in the USA and around the world (Christie 2011; Yusen 2010). In those under 18 years of age, CF, with its associated bronchiectasis and obstructive lung disease, was the indication in about 70% of lung transplants both in the USA and around the world (Aurora 2009; Yusen 2010). Most of these paediatric transplants occurred in adolescents (aged between 6 and 18 years of age).

The overall 1-year, 5-year, and 10-year unadjusted mean survival rates after lung transplantation in the USA have been reported to be approximately 83%, 54%, and 29% respectively (OPTN 2009). Among people with CF or immunodeficiency disorders, these rates were reported to be approximately 87%, 57%, and 38% respectively. Similar rates have been reported around the world (Christie 2011). Among the various indications for transplantation, CF has been associated with the highest rates of post-lung transplant survival (Christie 2011; Yusen 2010).

Bilateral lung transplants have been associated with higher unadjusted survival rates at 5-years and 10-years post-transplant compared to single lung transplants (Christie 2011; OPTN 2009). However, differences in rates of survival by procedure type need to be interpreted with caution because survival is influenced by multiple clinical factors that inform the decision to perform a particular procedure type (Christie 2011). Lung transplants can also be classified based on whether the donor is living or deceased.

Deceased donors can be further classified as donation after brain death (DBD) donors or donation after cardiac death (DCD) donors. It is extremely rare that DCD donor lungs are used (1% in 2008) (OPTN 2009).

Whatever the type of lung transplant, graft rejection is an important potential consequence. Graft rejection has been classified into the following three clinically and histologically distinct categories (King-Biggs 1997).

Hyperacute rejection

This usually arises within minutes after perfusion of the newly grafted organ is established (King-Biggs 1997). It is an antibody-mediated reaction in response to blood group antigens, human leukocyte antigens (HLA), and other antigens that cause cell-mediated injury. Widespread testing for compatibility of donors and recipients in terms of blood group antigens, HLA, and other antigens has virtually led to the elimination of this complication (King-Biggs 1997).

Acute rejection

This is a cell-mediated inflammatory response in the recipient due to HLA antigens of the donor (King-Biggs 1997). The major effector cells are T-cells. The classical clinical picture of acute rejection includes symptoms such as dyspnoea, fatigue, and dry cough; and signs such as low-grade fever, a drop in oxygenation greater than 10 mm Hg from baseline, development of new or changing radiographic infiltrates, and a decrease in forced expiratory volume in one second (FEV₁) greater than 10% from baseline. The most common differential diagnosis in the early post-operative period is infection (King-Biggs 1997). One out of every four acute rejection episodes occurs in the first month after transplant surgery. However, acute rejection remains an ongoing risk during the life of the transplanted organ (Hopkins 2002). Although currently available immunosuppressive agents adequately control episodes of acute rejection once they occur (Hopkins 2008), almost 80% of lung transplant recipients have been reported to suffer at least one acute rejection episode in the first month after surgery (Hopkins 2002).

Chronic rejection (obliterative bronchitis or bronchiolitis obliterans syndrome (BOS))

This usually occurs months to years after transplantation (King-Biggs 1997). It is characterised by progressive airflow obstruction that is often disabling (Paradis 1993). Chronic rejection occurs due to a complex immuno-pathogenic process, possibly involving sustained T-cell activation by donor major histocompatibility complex (MHC) and other antigens (Hopkins 2008) as well as non-immune factors. Current immunosuppressive protocols have not been sufficient to adequately prevent and treat this complication. It remains the major cause of late graft rejection following lung transplantation (Hopkins 2008).

It is worth noting that the terms acute and chronic rejection refer to the immunological process and not their period of occurrence (Hopkins 2008). Graft rejection and non-cytomegalovirus (non-CMV) infections have been reported to be the predominant causes of significant death among transplant recipients (Christie 2011).

Description of the intervention

Immunosuppressive therapy is needed to prevent episodes of graft rejection and thus significantly reduces morbidity and mortality in all people with lung transplantation.

Immunosuppressive therapy has been defined as therapy used to decrease the body's immune response, such as drugs given to prevent transplant rejection ([National Cancer Institute 2010](#)). There are a number of classes of these drugs acting on different components of the immune system. The main classes of immunosuppressive drugs currently being used during and after lung transplantation are listed below.

1. Polyclonal anti-lymphocyte antibodies

Included in this class are anti-lymphocyte globulin (ALG) and anti-thymocyte globulin (ATG), each of which could be either horse- or rabbit-derived.

2. Monoclonal anti-lymphocyte antibodies

Included in this class is the monoclonal anti-CD3 antibody (murmonab-CD3) which is mouse-derived and alemtuzumab which is a recombinant DNA-derived humanised monoclonal antibody. Alemtuzumab is currently approved for use in B-cell chronic lymphocytic leukaemia (B-CLL).

3. Interleukin-2 (IL-2) receptor antagonists

Included in this class are daclizumab and basiliximab which are chimeric (human or mouse) monoclonal antibodies.

4. Calcineurin inhibitors

These include cyclosporin A (CsA) which is a cyclic peptide produced by the fungus *Tolypocladium inflatum* and tacrolimus (Tac) which is a hydrophobic macrocyclic lactone derived from the actinomycete *Streptomyces tsukubaensis*.

5. Cell cycle inhibitors

These include azathioprine which is a nucleoside analogue and mycophenolate mofetil (MMF) which is a prodrug of mycophenolic acid (MPA).

6. Corticosteroids

These include prednisone (prednisolone) and methylprednisolone.

7. Mammalian target of rapamycin (mTOR) inhibitors

These include sirolimus (rapamycin) which is a macrolide antibiotic produced by the actinomycete *Streptomyces hygroscopicus*, and everolimus. Everolimus is a derivative of sirolimus but with higher oral bioavailability and shorter half-life.

Immunosuppressive therapy after lung transplantation usually consists of initial induction followed by maintenance regimens to prevent rejection.

Induction immunosuppressive therapy refers to the strategy of prophylactic use of immunosuppressive drugs during the early post-transplant period ([Knoop 2003](#)). The principle of induction therapy is to provide the strongest immunosuppression during the first few weeks following transplantation when the risk for rejection is at the maximum. The use of induction immunosuppressive therapy is associated with significantly higher survival after lung

transplantation ([Christie 2011](#)). Biological agents best suited to induction therapy are those that cause profound and expedient depletion in the activation of T-lymphocytes. These include agents from the following classes: polyclonal anti-lymphocyte antibodies; monoclonal anti-lymphocyte antibodies; and interleukin-2 (IL-2) receptor antagonists ([Knoop 2003](#)).

Maintenance immunosuppressive therapy is geared towards the long-term prevention of episodes of acute and chronic graft rejection ([Knoop 2003](#)). The principle of maintenance therapy is to provide effective long-term prevention against rejection through combination therapy that minimises adverse effects of individual drugs. The aims of combination therapy are to maximise synergism, achieve multi-pathway inhibition of lymphocyte activation, and minimisation of cumulative toxicity ([Hopkins 2008](#)). The most commonly used combinations are triple-drug regimens including a calcineurin inhibitor, a cell cycle inhibitor, and a corticosteroid ([Knoop 2003](#)).

How the intervention might work

The mechanisms of action of each class of immunosuppressive drugs are described below:

1. Polyclonal anti-lymphocyte antibodies

The antibodies ALG and ATG (from either horse or rabbit sources) act by targeting numerous antigens on lymphocyte cell surfaces, thereby depleting the levels of circulating lymphocytes ([Knoop 2003](#)).

2. Monoclonal anti-lymphocyte antibodies

Murmonab-CD3 acts by specifically targeting the CD-3 complex, which is a series of proteins associated with the T-lymphocyte antigen receptor (TCR) ([Knoop 2003](#)). This binding causes opsonization and complement-mediated T-cell depletion ([Cosimi 1981](#)). Alemtuzumab binds to CD-52, an antigen present on the surface of T and B lymphocytes ([Wierda 2005](#)). This binding causes antibody-dependent lysis of lymphocytes.

3. Interleukin-2 (IL-2) receptor antagonists

The IL-2 plays a key role in T-cell activation and acute graft rejection ([Hopkins 2008](#)). It acts by binding to a high-affinity receptor located on the surface of T-cells, thus blocking IL-2 induced T-cell proliferation ([Knoop 2003](#)). Both daclizumab and basiliximab act by targeting the alpha chain (Tac subunit) of the IL-2 receptor ([Hopkins 2008](#)).

4. Calcineurin inhibitors

Calcineurin, through its enzymatic (phosphatase) activity in the cytoplasm of the cell, is critical for the transcription of cytokines like IL-2, IL-3, IL-4, IL-5, interferon- γ , tumour necrosis factor- α (TNF- α), and granulocyte/macrophage colony-stimulating factor (GM-CSF) ([Knoop 2003](#)). By binding with cyclophilin in the cytoplasm of the cell, CsA acquires its active form. This in turn inactivates calcineurin causing the downstream effect of reduced T-cell activation. Tac acts in a similar manner to CsA, but instead of binding with cyclophilin, it binds with FK-binding proteins (FKBPs) in the cytoplasm.

5. Cell cycle inhibitors

Azathioprine, a nucleoside analogue, acts by inhibiting deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and *de*

de novo purine synthesis (Hopkins 2008; Knoop 2003). This affects the proliferation of T- and B-lymphocytes without affecting the transcription of cytokines. MMF, which is not a nucleoside analogue, acts by converting to its active form MPA; MPA is a reversible inhibitor of inosine monophosphate dehydrogenase (IMPD), which is the rate-limiting enzyme in the *de novo* purine synthetic pathway (Knoop 2003; Hopkins 2008).

6. Corticosteroids

Corticosteroids act by blunting the activation and proliferation of T-lymphocytes, diminishing the secretion of cytokines through reduced cytokine gene transcription, and directly lysing immature T-lymphocytes (King-Biggs 1997; Hopkins 2008).

7. Mammalian target of rapamycin (mTOR) inhibitors

The mechanism of action of sirolimus (rapamycin) is similar to Tac. However, although sirolimus binds with FKBP-12 (similar to Tac), it inhibits a kinase called mTOR (instead of calcineurin that Tac inhibits) (Knoop 2003; Hopkins 2008). The inhibition of mTOR in turn inhibits the T-cell proliferative response to cytokines and growth factors.

Why it is important to do this review

Immunosuppressive therapy is generally accepted as a necessary therapy to prevent graft rejection post transplantation, including lung transplantation. While much of the research in immunosuppressive drug therapy has focused on the general population of lung transplant recipients, little is known about the comparative effectiveness and safety of these agents in people with CF. There is considerable variability in the use of immunosuppressive agents after lung transplantation in CF (Christie 2011; Lischke 2007). Variation exists for both induction and maintenance immunosuppressive therapy (Christie 2011).

The International Society for Heart and Lung Transplantation (ISHLT) maintains an international registry on heart and lung transplantation, in both CF and those who don't have CF (ISHLT 2013). According to ISHLT registry data, about one in six (16.8%) of the 30,673 lung transplantations performed between January 1995 and June 2010 were in people with CF (Christie 2011). The use of induction immunosuppressive therapy after lung transplantation has increased in recent times, with 60% of people receiving it in 2010 compared to just 24% in 1997. In 2010, 41% of people received IL-2 receptor antagonists, 15% received polyclonal anti-lymphocyte antibodies, and 8% received monoclonal anti-lymphocyte antibodies. The ISHLT registry data also indicate that, between 2002 and 2010, the use of IL-2 receptor antagonists in induction immunosuppressive therapy was associated with lower reported incidence of acute rejection compared to no induction or use of polyclonal anti-lymphocyte antibodies (Christie 2011). However, such data obtained from registries need to be interpreted with caution because of potential limitations. These include selection bias, missing data, reporting delays, and the fact that the data are not obtained from experimental clinical studies (Izquierdo 2000; Nathan 2007).

According to the ISHLT registry data from 2002 through 2007, the combination of a calcineurin inhibitor + a cell cycle inhibitor + a corticosteroid was the most commonly used regimen during maintenance immunosuppressive therapy (Christie 2011). However, there was no consensus on agents to be used within

these classes. The combination of Tac + MMF + prednisone was the most commonly used (about 45% of transplant recipients at one year and about 34% of recipients at five years post-transplant). The next most commonly used combination was Tac + azathioprine + prednisone (about 22% of recipients at one year and about 19% of recipients at five years post-transplant). Other combinations in use included CsA + MMF + prednisone; CsA + azathioprine + prednisone; sirolimus (rapamycin) + calcineurin inhibitors + prednisone; and sirolimus (rapamycin) + cell cycle inhibitors + prednisone. CsA-based regimens were associated with the highest rates of acute rejection, being highest for those receiving the combination of CsA + azathioprine + prednisone. Tac-based regimens were associated with the lowest rates of acute rejection, being lowest for those receiving the combination of Tac + MMF + prednisone (Christie 2011).

In addition, people with CF suffer from high rates of chronic infections and usually receive multiple treatments for a variety of disease manifestations (Ratjen 2003). All these factors necessitate the study of immunosuppressive agents specifically in people with CF.

This is an update of a previously published review (Saldanha 2013; Saldanha 2015).

OBJECTIVES

The objective of this review is to assess the effects of immunosuppressive drug therapy to prevent rejection following lung transplantation in people with CF. In particular, this review aims to assess the effects of individual drugs or combinations of individual drugs compared to placebo or other individual drugs or combinations of individual drugs.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled studies.

Types of participants

Individuals with CF following lung transplantation (including lobe, single-lung, and bilateral transplants) or heart-lung transplantation.

Types of interventions

We planned to include studies of comparisons of individual drugs (e.g. cyclosporine (CsA), tacrolimus (Tac), sirolimus (rapamycin), mycophenolate mofetil (MMF)) or combinations of individual drugs to placebo or other individual drugs or combinations of other individual drugs. We also planned to include comparisons of two drugs within the same class (e.g. daclizumab versus basiliximab).

Types of outcome measures

We planned to assess the following outcome measures.

Primary outcomes

1. Episodes of rejection
 - a. hyperacute rejection
 - b. acute rejection
 - c. chronic rejection (bronchiolitis obliterans syndrome (BOS))
2. Mortality
3. Quality of life (QoL) - all instruments, of any validity, that measure the ability of participants to perform activities of daily living (including but not limited to the Cystic Fibrosis Questionnaire-Revised version (CFQ-R) (Quittner 2009) and the Cystic Fibrosis Quality of Life Questionnaire (CFQoL) (Gee 2000))

Secondary outcomes

1. Opportunistic infections (including cytomegalovirus (CMV) and non-CMV infections)
2. Adverse events (e.g. nephrotoxicity, cardiotoxicity, post-transplant development of diabetes mellitus)
3. Lung function
 - a. forced expiratory volume at one second (FEV₁) (both in litres and per cent predicted)
 - b. forced expiratory volume (FVC) (both in litres and per cent predicted)
 - c. mid-expiratory flow (FEF_{25-75%})
4. Individual preference
5. Sputum weight (g)
 - a. dry weight
 - b. wet weight
6. Oxygen saturation:
 - a. arterial blood gas
 - b. pulse oximetry
 - c. transcutaneous oximetry
7. Incidence of co-morbidities
 - a. hypertension
 - b. diabetes mellitus
 - c. hyperlipidaemia
 - d. renal dysfunction
8. Hospitalisation (*post hoc* change)

Search methods for identification of studies

Searches were not limited by date, language or publication status.

Electronic searches

We identified relevant studies from the Group's Cystic Fibrosis Trials Register using the terms: transplantation AND lung AND immunosuppressant.

The CF Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), weekly 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 CF 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 Cochrane Cystic Fibrosis and Genetic Disorders Group [website](#).

Date of search: 30 May 2018.

We also searched the www.clinicaltrials.gov registry and the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) (<http://apps.who.int/trialsearch/>) on May 29, 2018 to obtain information on unpublished and ongoing studies.

Searching other resources

If we identify eligible studies for updates of the review, we will search the reference lists of included articles and other relevant studies and reviews to identify additional studies. We will also contact the authors of the included articles. We also handsearched the *Journal of Heart and Lung Transplantation* (for the years 2012, 2013, and 2014), which is the official publication of the International Society for Heart and Lung Transplantation (ISHLT).

Data collection and analysis

Selection of studies

We used a two-tier screening process to identify relevant articles. Initially, we screened the titles and abstracts of articles identified through searching and obtained the full text versions of those considered potentially relevant. We then screened the full text articles to identify those studies which should be included in the review and are eligible for data abstraction. Two review authors (IJS, OA) independently screened each article. We resolved any disagreements by consensus.

We planned to include studies which either included people with CF exclusively or which included at least some people with CF. However, this second kind of study would only be included provided we were able to abstract from the article, or obtain from its authors, specific data on outcomes related to those with CF.

Data extraction and management

We imported search results into a reference management software (Procite, Thomson Reuters, New York, NY). We then screened citations and tracked results of the screening using the reference management software. We designed custom data abstraction forms to abstract information from eligible review articles and planned for one author (IJS) to abstract data and a second author (OA) to review the abstracted data for completeness and accuracy. We intended to resolve any disagreements through consensus or consultation with a third reviewer (KAR). One author (IJS) would then have entered the data into RevMan (RevMan 2014).

We planned to group eligible studies together based on time of outcome assessment. We planned to consider outcomes as immediate if up to one week duration; short term if more than one week and up to one month duration; medium term if more than one month and up to six months duration; and long term if more than six months duration. If studies reported data at multiple time points within an interval, we planned to analyse these separately if appropriate.

Assessment of risk of bias in included studies

We planned to assess the risk of bias in included studies through assessment of random sequence generation; allocation concealment; blinding of the study participants and personnel,

blinding of outcome assessors; incomplete outcome data; selective reporting; and other sources of bias (compliance assessment; washout reporting; intention-to-treat analysis; and loss to follow up). We would have assessed studies using each of these criteria as having high, low, or unclear risk of bias. Two review authors (IJS, OA) would have independently applied the methods for evaluating the risk of bias described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We intended to resolve any disagreements through consensus or consultation with a third review author (KAR).

Measures of treatment effect

We planned to analyse continuous outcomes using the mean difference (MD) (or we would have calculated the standardised mean difference (SMD) if different scales of measurement have been used) and dichotomous outcomes using the risk ratio (RR). We planned to present all outcomes with associated 95% confidence intervals (CIs).

Unit of analysis issues

When conducting analyses, we planned to take into consideration the level at which randomisation occurred (Sterne 2011). Randomised controlled studies with parallel group designs are studies where individuals are independently randomised to intervention groups. In cross-over studies, individuals are randomised to more than one intervention. However, this design is not suitable for most immunosuppressive drug studies because the clinical outcomes of transplant recipients or graft survival may be highly dependent on the initial anti-rejection therapy (Leonard 2001). We therefore only planned to include first-arm data from cross-over studies.

Dealing with missing data

In the event of missing, incomplete, or unclear data, we intended to contact the original investigators. This includes unreported outcomes, missing participants, and missing statistics (such as standard deviations). Where the necessary data for analysis was not available, we planned to provide a narrative summary of the studies.

Assessment of heterogeneity

We intended to assess clinical heterogeneity by considering variability in the participants, interventions, and comparisons in the included studies. We also intended to assess statistical heterogeneity within each outcome between the comparisons using the χ^2 test and I^2 statistic (Higgins 2003). Under the null hypothesis of homogeneity, we would have considered a P value of less than 0.10 to indicate the presence of heterogeneity in the χ^2 test (Sterne 2011). We would have interpreted the results with care since the test could have low or high power. Low power is common when studies have a small sample size or there are a small number of studies, which may result in the lack of detection of heterogeneity when it is present. High power is common when there are many studies being analysed, resulting in the detection of heterogeneity that may be insignificant. The I^2 statistic measures the proportion of inconsistency in individual studies that cannot be explained by sampling error. In this test the degree of heterogeneity is quantified. The values of I^2 lie between 0 and 100%. We planned to consider I^2 results less than 40% to indicate that heterogeneity might not be important; between 30% and 60% to indicate that

heterogeneity may be moderate; between 50% and 90% to indicate that heterogeneity may be substantial; and between 75% and 100% to indicate considerable heterogeneity (Deeks 2011).

Assessment of reporting biases

If we had included more than 10 studies, we planned to assess reporting bias among the studies using the funnel plot method discussed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). If asymmetry had been present, we would have explored possible causes including publication bias, risk of bias, outcome reporting bias, and true heterogeneity. Outcome reporting bias can occur when studies measure outcomes, but do not publish all of them. This can lead to misleading results (Kirkham 2010). We planned to compare the 'Methods' section of the paper to the 'Results' section to ensure all outcomes are reported. If we had suspected outcome reporting bias, we would have contacted study authors for the data.

Data synthesis

We planned to enter data abstracted from included studies into RevMan 5.3 (RevMan 2014). If heterogeneity was low, as indicated by an I^2 result less than 30%, we planned to use a fixed-effect model to synthesise the results. If heterogeneity was moderate, substantial, or considerable, as indicated by an I^2 of 30% or higher, we planned to use a random-effects model to synthesise the results. We aimed to synthesise results by combining studies of individual drugs as well as combining studies of drugs within the same class of immunosuppressants. If we had found it inappropriate to conduct meta-analysis, we would have provided a narrative synthesis of the available data.

Subgroup analysis and investigation of heterogeneity

If the review had included at least 10 studies, we planned to investigate any heterogeneity through the following subgroup analyses:

1. age (children (up to 18 years old) versus adults);
2. type of donor (among the deceased donors, DBD donors versus DCD donors);
3. extent of tissue being transplanted (lobe, single lung, and bilateral lung transplants);
4. pre-transplant lung function (FEV₁, % predicted over 60%, 41% to 59%, 21% to 40%, under 20%);
5. pre-transplant ventilator status (on versus off ventilation).

Sensitivity analysis

We planned to perform sensitivity analyses to identify the effects of unpublished studies, study size (stratified by sample size), study design (cross-over versus parallel studies), allocation concealment (high risk of bias versus low risk of bias), participant blinding (high risk of bias versus low risk of bias), assessor blinding (high risk of bias versus low risk of bias), and loss to follow up (high risk of bias versus low risk of bias) on the results.

Summary of findings and assessment of the certainty of the evidence

If we had been able to include eligible studies in this systematic review, we planned to develop a summary of findings table for each comparison presented in the review in accordance with GRADE

guidelines. In that event, we intended to include the following seven outcomes in the summary of findings table:

1. Hyperacute rejection
2. Acute rejection
3. Chronic rejection (BOS)
4. Mortality
5. QoL
6. Opportunistic infections
7. Adverse events

RESULTS

Description of studies

Results of the search

We identified 14 records to 11 studies. Of the 14 records, we identified 10 from the electronic search and four by handsearching. We excluded six records to six studies at the title and abstract screening stage. The eight remaining records (seven full-text articles and the single abstract) described five randomised controlled studies. We excluded these eight records at the full-text screening stage because the investigators of the studies did not report any CF-specific information ([Figure 1](#)).

Figure 1. Study flow diagram.

Included studies

No studies were included.

Excluded studies

At the full-text screening stage, we excluded eight records describing five randomised controlled studies because the investigators did not report results specific to participants with CF (Bhorade 2011; Iacono 2006; Glanville 2015; Treede 2012; Doyle 2001). The earliest study was a Phase I randomised study evaluating the pharmacokinetics and safety of RAD, a macrolide, in 20 participants that included eight participants with CF (Doyle 2001). The second study compared 300 mg of inhaled cyclosporin A with aerosol placebo three days a week for the first two years after lung transplantation. In addition to nine participants with CF, the study included 45 participants with other diagnoses including chronic obstructive pulmonary disease (COPD) or emphysema, idiopathic pulmonary fibrosis (IPF), pulmonary hypertension, and connective tissue disease (Iacono 2006). The third study compared sirolimus to azathioprine in 181 lung transplant recipients, including some with CF (Bhorade 2011). The fourth study compared tacrolimus with cyclosporine in 249 lung transplant participants, including 62 with CF (Treede 2012). The most recent study compared mycophenolate sodium to everolimus (both arms in combination with CsA) in 165 lung transplant recipients, including some with CF (Glanville 2015). However, all results for all five of these studies were only available for all participants combined (and not specifically for participants with CF).

We have contacted the investigators to obtain the information specific to participants with CF, but have not received the requested information.

Risk of bias in included studies

No studies were included in this review.

Effects of interventions

No studies were included in this review.

DISCUSSION

Summary of main results

This systematic review identified five randomised controlled studies; one comparing inhaled cyclosporin A versus placebo aerosol (Iacono 2006), one comparing sirolimus versus azathioprine (Bhorade 2011), one comparing tacrolimus versus cyclosporine (Treede 2012), one comparing mycophenolate sodium versus everolimus (Glanville 2015), and another comparing differing dosing schedules of RAD (a macrolide) (Doyle 2001). However, these five studies could not be included in the review because the investigators did not report CF-specific results. We have contacted the investigators for this information, but have not received it. Thus, it is not possible to comment on the use of any of the immunosuppressive drugs among people with CF.

Overall completeness and applicability of evidence

We did not identify any eligible studies with extractable information on the use of immunosuppressive drugs among people with CF.

Quality of the evidence

As no studies were included in the review, we could not assess the quality of the evidence.

Potential biases in the review process

Given our comprehensive search strategy, it is unlikely that we have missed any relevant studies. However, we did identify studies that we could not include because the investigators did not report CF-specific results. Our attempts to obtain this information have not been successful.

Agreements and disagreements with other studies or reviews

As no study was included in the review, we could not assess the agreement or disagreement with other studies. A 2013 Cochrane Review comparing tacrolimus with cyclosporine in all lung transplant recipients (not restricted to people with CF) reported no significant difference in mortality or risk of acute rejection (Penninga 2013). However, participants receiving tacrolimus experienced a lower risk of BOS, RR 0.46 (95% CI 0.29 to 0.74) and arterial hypertension, RR 0.67 (95% CI 0.50 to 0.89). Participants receiving tacrolimus experienced higher risk of diabetes mellitus as an adverse event, RR 4.43 (95% CI 0.75 to 26.05). However, the investigators of the review noted the high risk of bias and small number of included studies ($n = 3$) in the review (Penninga 2013).

AUTHORS' CONCLUSIONS

Implications for practice

The lack of currently available evidence specific to people with cystic fibrosis (CF) makes it impossible to draw conclusions about the comparative efficacy and safety of the various immunosuppressive drugs among lung transplant recipients with CF.

It is generally accepted that, as for all lung transplant recipients, immunosuppressive therapy is needed to prevent episodes of graft rejection among those with CF. The use of immunosuppressive therapy prevents significant morbidity and mortality among lung transplant recipients. However, the current evidence base does not inform the choice of use of one immunosuppressive drug versus another.

Implications for research

Well-designed, adequately-powered, multicentre randomised controlled studies are required to provide evidence for the benefit and safety of the use of immunosuppressive therapy among people with CF after lung transplantation.

ACKNOWLEDGEMENTS

We would like to acknowledge the previous work of Naomi McKoy who contributed greatly to previous versions of this review.

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necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bhorade 2011	Unable to extract CF-specific information. Authors contacted, but no information received.
Doyle 2001	Unable to extract CF-specific information. Authors contacted, but no information received.
Glanville 2015	Unable to extract CF-specific information. Authors contacted, but no information received.
Iacono 2006	Unable to extract CF-specific information. Authors contacted, but no information received.
Treede 2012	Unable to extract CF-specific information. Authors contacted, but no information received.

CF: cystic fibrosis

APPENDICES

Appendix 1. Glossary

Term	Explanation
chimeric antibody	A hybrid substance combining antibodies and parts of antibodies with the potential to track down and illuminate remote and microscopic tumours. It is less easily rejected by the body's immune system than the ordinary monoclonal antibody.
cyclic peptide	An unusual class of compounds that range from antibiotics, such as bacitracin and polymyxin B, to the immunosuppressant drug cyclosporin. They can also be toxins. They tend to survive the human digestive process and can bind proteins in the cell where traditional drugs cannot.
dyspnoea	Laboured or difficult breathing, shortness of breath, or breathlessness.
hydrophobic	Repelled by water.

(Continued)

kinase	A type of enzyme that transfers phosphate groups from high-energy donor molecules, such as adenosine triphosphate (ATP), to specific substrates.
lysis	The breaking down of a cell.
macrocyclic lactone	Chemical compounds that represent the main treatment for parasitic diseases of animals.
monoclonal antibody	A protein substance which is produced in the laboratory by a single population of cells.
non-cytomegalovirus infections	Infections caused by organisms other than cytomegalovirus (CMV).
nucleoside analogue	A range of antiviral products used to prevent viral replication in infected cells.
opsonization	The process of making bacteria more liable to destruction by phagocytes (cells that ingest and destroy other cells, microorganisms, or other foreign matter in the blood and tissues).
polyclonal antibodies	Antibodies that are obtained from different B-cell resources.
radiographic infiltrates	A collection of cells not usually present in that area visible through radiography.
synergism	Interaction of discrete agents (such as drugs) such that the total effect is greater than the sum of the individual effects.
T-cells	Cells which belong to a group of white blood cells known as lymphocytes, and play a central role in cell-mediated immunity.

WHAT'S NEW

Date	Event	Description
6 May 2021	Review declared as stable	Due to a lack of research in this area, we will no longer be updating this review.

HISTORY

Protocol first published: Issue 11, 2011

Review first published: Issue 12, 2013

Date	Event	Description
30 May 2018	New search has been performed	<p>A new search of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register identified three new references; one was excluded at abstract screening and two were excluded from the review (Doyle 2001; Treede 2012).</p> <p>In line with current Cochrane guidance, we have added that we will use GRADE to generate summary of findings tables if we are able to include studies in future reviews.</p>

Date	Event	Description
30 May 2018	New citation required but conclusions have not changed	As we have not been able to include any new studies at this update, our conclusions remain the same.
2 November 2015	New citation required but conclusions have not changed	As previously stated in the amendment published in March 2015, Naomi McKoy has stepped down from the author team. The identification of the single reference at this update has not led to any change in conclusions.
2 November 2015	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register identified a single new reference (Glanville 2015). This reference describes a study that is otherwise eligible, but data were not provided specifically for people with CF. We have currently excluded the study, but we contacted the authors to obtain CF-specific information and will re-assess the study once these data are available.
31 March 2015	Amended	Naomi McKoy has been removed from the author byline.

CONTRIBUTIONS OF AUTHORS

TASK	WHO WILL UNDERTAKE THE TASK?
<i>Protocol stage:</i> draft the protocol	All authors
<i>Review stage:</i> select which studies to include (2 + 1 arbiter)	All authors
<i>Review stage:</i> extract data from studies (2 people)	Ian Saldanha and Oluwaseun Akinyede
<i>Review stage:</i> enter data into RevMan	Ian Saldanha
<i>Review stage:</i> carry out the analysis	Ian Saldanha
<i>Review stage:</i> interpret the analysis	All authors
<i>Review stage:</i> draft the final review	All authors
<i>Update stage:</i> update the review	All authors

DECLARATIONS OF INTEREST

The authors have no relevant conflicts of interest to declare.

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Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Original review 2013

Following the peer review process:

1. we added 'Hospitalisation' as a secondary outcome;
2. we deleted the planned subgroup analysis "deceased versus living donor";
3. added two new proposed subgroup analyses:
 - pre-transplant LAS (higher versus lower)
 - pre-transplant ventilator status (on versus off ventilation)

Update 2017

We will include a summary of findings table for each comparison presented in the review if further updates of this review include any studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Cystic Fibrosis [*surgery]; Graft Rejection [*prevention & control]; Immunosuppressive Agents [*therapeutic use]; *Lung Transplantation

MeSH check words

Humans