

Lupus kidney disease and immunosuppressive agents Summaries and decision aid

How well do immunosuppressive agents, such as cyclophosphamide plus steroids, work to treat lupus kidney disease (SLE nephritis) and how safe are they?

To answer this question, scientists found and analysed 2 reviews of the literature and 2 more studies testing medications in people with lupus kidney disease. People received either pills (by mouth, oral) or injections (IV) of medications for kidney lupus disease. These studies provide the best evidence today.

What is lupus kidney disease and how is it treated?

SLE (systemic lupus erythematosus) or simply “lupus” is a group of diseases in which the body’s immune system fights or attacks itself. Lupus can cause swelling, pain, and damage to many organs of the body such as the skin, heart, lungs, brain and kidneys. When people with lupus have kidney problems or kidney disease, it is called SLE nephritis or lupus kidney disease. Drugs are prescribed to prevent kidney failure. Corticosteroids such as prednisone, are used with immunosuppressive agents or cytotoxics, such as cyclophosphamide (Cytoxan), azathioprine (Imuran) or mycophenolate mofetil (Cellcept).

How well did cyclophosphamide plus steroids work to treat lupus kidney disease?

The reviews and studies showed that people who in addition to prednisone, received cyclophosphamide or azathioprine had less of a decrease in kidney function, were less likely to develop kidney failure or die from kidney disease than people who received prednisone alone. Cyclophosphamide or azathioprine alone showed the same improvements seen with prednisone alone. One of the reviews also found that oral azathioprine and oral cyclophosphamide worked just as well as the other.

What were the side effects?

Side effects such as menstrual periods stopping in women (amenorrhoea), infections, death of bone tissue, bone loss, cervical dysplasia (precancerous change to cells in the cervix), and death due to complications from infections may occur when taking steroids and immunosuppressive agents.

What is the bottom line?

There is “Silver” level evidence that taking steroids (such as prednisone) with immunosuppressive agents (cyclophosphamide or azathioprine) is better than taking corticosteroids alone to improve kidney function and survival in patients with lupus kidney disease.

Side effects of cyclophosphamide and azathioprine, include infections, cancer, and death from complications of the drugs.

From Schiffenbauer J, Chakravarty E, Strand V. Systemic lupus erythematosus. In: *Evidence-based Rheumatology*, London, BMJ Books, 2003.

How well do immunosuppressive agents, such as cyclophosphamide, plus steroids, work to treat lupus kidney disease (SLE nephritis) and how safe are they?

What is lupus kidney disease and how is it treated?

SLE (systemic lupus erythematosus) or simply “lupus” is a group of diseases in which the body’s immune system does not work properly. Normally, the body’s immune system fights or attacks germs but in lupus the body starts to attack itself. Lupus can cause swelling and damage to many organs of the body such as the skin, heart, lungs, brain and kidneys. Lupus occurs in cycles, where there are periods of pain and illness or periods of little or no pain and illness (remission). When people with lupus have kidney problems or kidney disease, it is called SLE nephritis.

Drugs are prescribed to treat the kidney disease to prevent the kidneys from failing. The drugs can decrease swelling in the kidney and control the immune system. Corticosteroids such as prednisone are used with immunosuppressive agents or cytotoxics, such as cyclophosphamide (Cytoxan) and azathioprine (Imuran), or mycophenolate mofetil (Cellcept). Most of these drugs can be taken by mouth or by injection (IV) and sometimes alone or in combination. Unfortunately, these drugs can cause side effects that can cause damage in the body and therefore it is important to determine which medications taken alone or in combination work and which are safe.

How did the scientists find the information and analyse it?

The scientists searched for studies and reviews of the medical literature that examined the treatment of lupus kidney disease. Not all studies and reviews found were of a high quality and so only those studies that met high standards were selected.

Which high quality studies and reviews were examined in this summary?

There were two reviews of the literature and 2 more studies examined in this summary. Two high quality studies included in the one review of the literature are also described. All patients tested had lupus kidney disease.

- One review examined 8 studies that compared the effects of prednisone and a placebo to prednisone with an immunosuppressive agent such as cyclophosphamide or azathioprine.
- The other review examined 19 studies that compared the effects of prednisone to prednisone plus one immunosuppressive agent (cyclophosphamide or azathioprine) or to azathioprine alone.
- One study in the above review compared the effects of prednisone to prednisone and cyclophosphamide in 13 patients over 10 weeks. And the other study compared the effects of prednisone to prednisone plus cyclophosphamide or prednisone plus azathioprine in 38 patients over 10 weeks.
- The two recent studies compared 82 patients receiving methylprednisolone (MP) or cyclophosphamide; or MP plus cyclophosphamide over 1 year and over 11 years.

How well did cyclophosphamide plus steroids work to treat lupus kidney disease?

The first review showed that patients who received, in addition to prednisone, oral cyclophosphamide or azathioprine had less decrease in kidney function, were less likely to develop kidney failure or die from kidney disease than patients who received prednisone alone. Patients with “diffuse proliferative

glomerulonephritis" (a form of damage in the kidney) had the most improvement with cyclophosphamide plus prednisone or azathioprine plus prednisone. Cyclophosphamide or azathioprine alone showed the same improvements seen with prednisone alone.

The second review showed that patients who received, in addition to prednisone, cyclophosphamide or azathioprine were less likely to develop kidney failure or die from kidney disease than patients who received prednisone alone. This review found the same results as the first review and also found that azathioprine and cyclophosphamide worked just as well as the other.

Specifically, two high quality Gold studies in the review showed that after 10 weeks of treatment:

- more patients improved on more tests for kidney function with prednisone plus cyclophosphamide than with prednisone plus a placebo
- other symptoms of lupus (for example: rashes, fever, arthritis, mouth sores, and swelling around the lungs and heart) went away (in 5 out of 9 patients) or did not occur in patients who received prednisone plus cyclophosphamide. But the symptoms stayed or did occur (6 out of 15 patients) in patients receiving prednisone alone.

The results of the best two most recent studies showed that after 1 year:

— **Renal remission (period of little or no swelling in the kidney) occurred in**

- 26 out of 100 patients receiving methylprednisone alone
- 48 out of 100 patients receiving cyclophosphamide alone
- 61 out of 100 patients receiving methylprednisone and cyclophosphamide together.

— **Improved kidney function occurred in**

- 37 out of 100 patients receiving methylprednisone alone
- 70 out of 100 patients receiving cyclophosphamide alone
- 89 out of 100 patients receiving methylprednisone and cyclophosphamide together.

What were the side effects?

Side effects such as menstrual periods stopping in women (amenorrhoea), infections, death of bone tissue (avascular necrosis), bone loss (osteoporosis), cervical dysplasia (precancerous change to cells in the cervix), and death due to complications from infections may occur when taking steroids and immunosuppressive agents.

After 1 year, more patients had side effects when taking methylprednisone and cyclophosphamide together compared to patients taking either drug on its own.

In the best study testing cyclophosphamide plus methylprednisone for 1 year, side effects occurred in:

- 7 out of 100 patients receiving methylprednisone alone
- 41 out of 100 patients receiving cyclophosphamide alone
- 43 out of 100 patients receiving methylprednisone and cyclophosphamide together.

What is the bottom line?

There is “Silver” level evidence that taking steroids (such as prednisone) with immunosuppressive agents (cyclophosphamide or azathioprine) is better than taking corticosteroids alone to improve kidney function and survival in patients with lupus kidney disease.

Side effects of cyclophosphamide and azathioprine, include infections, cancer, and death from complications of the drugs.

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Information for lupus kidney disease (SLE nephritis) and treatment

What is lupus kidney disease?

SLE (systemic lupus erythematosus) or simply “lupus” is a group of diseases in which the body’s immune system does not work properly. Normally, the body’s immune system fights or attacks germs but in lupus the body starts to attack itself. Lupus can cause swelling, pain and damage to many organs of the body such as the skin, heart, lungs, brain and kidneys. When people with lupus have kidney problems or kidney disease, it is called SLE nephritis.

Lupus usually occurs in cycles, where there are periods of pain and illness or periods of little or no pain and illness. If the swelling is not treated, it can cause permanent damage. In lupus kidney disease, pain and swelling in the kidney can cause permanent damage to the kidney that can lead to

- swollen feet and legs (water retention)
- kidneys stop working
- need for dialysis or kidney transplant
- death.

What can I do on my own to manage my disease?

- ✓ exercise
- ✓ avoid alcohol
- ✓ relaxation

What treatments are used for lupus kidney disease?

Three kinds of treatment may be used alone or together. The common (generic) names are shown below.

1. *Oral or IV corticosteroids*
 - Prednisone
 - Prednisolone
 - Methylprednisolone
2. *Immunosuppressive agents (cytotoxics)*
 - Azathioprine
 - Cyclophosphamide
 - Mycophenolate mofetil
3. *Alternative therapies*
 - Ciclosporin
 - IV immunoglobulins

What about other treatments I have heard about?

There is not enough evidence about the effects of some treatments. Other treatments may not work. For example:

- Plasmapheresis (may not work)
- LJP 394 (need more research)
- Dehydroepiandrosterone (DHEA) (need more research)

What are my choices? How can I decide?

Treatment for your disease will depend on your condition. You need to know the good points (pros) and bad points (cons) about each treatment before you can decide.

Lupus kidney disease (SLE nephritis) decision aid

Do I agree to take the recommended treatment of steroids (such as prednisone) plus cyclophosphamide?

This guide can help you make decisions about the treatment your doctor is asking you to consider.

It will help you to:

1. Clarify what you need to decide.
2. Consider the pros and cons of different choices.
3. Decide what role you want to have in choosing your treatment.
4. Identify what you need to help you make the decision.
5. Plan the next steps.
6. Share your thinking with your doctor.

Step 1: Clarify what you need to decide What is the decision?

Do I agree to take the recommended treatment of steroids (such as prednisone) plus cyclophosphamide?

In addition to the dose of prednisone, cyclophosphamide may be taken as a pill daily or as an injection into the veins (IV).

When does this decision have to be made? Check ✓ one

within days within weeks within months

How far along are you with this decision? Check ✓ one

- I have not thought about it yet
- I am considering the choices
- I am close to making a choice
- I have already made a choice

Step 2: Consider the pros and cons of different choices

What does the research show?

Cyclophosphamide plus steroids is classified as: **Likely beneficial**

There is “Silver” level evidence from 2 reviews and 2 studies of people with lupus kidney disease who took immunosuppressive agents plus corticosteroids. The studies lasted for up to 10 weeks to 11 years. These studies found pros and cons that are listed in the chart below.

What do I think of the pros and cons of cyclophosphamide plus steroids?

1. Review the common pros and cons.
2. Add any other pros and cons that are important to you.
3. Show how important each pro and con is to you by circling from one (*) star if it is a little important to you, to up to five (*****) stars if it is very important to you.

PROS AND CONS OF CYCLOPHOSPHAMIDE PLUS STEROIDS	
PROS (number of people affected)	How important is it to you?
Improves symptoms of lupus kidney disease 61 out of 100 people had little or no symptoms	* * * * *
Improves other symptoms of lupus rashes, fever, mouth sores, and arthritis disappeared in 55 out of 100 people No one developed more symptoms of lupus while taking pills	* * * * *
Improves kidney function in 89 out of 100 people	* * * * *
Lowers chances of needing kidney dialysis or kidney transplantation	* * * * *
Other pros:	* * * * *
CONS (number of people affected)	How important is it to you?
Side effects: serious infections, hair loss, sore bladder, blood in urine, bone loss, death of bone tissue in 43 out of 100 people	* * * * *
Long term harms: cancer, diabetes, early menopause, bladder tumours, other cancers and death	* * * * *
Personal cost of medicine	* * * * *
Extra clinic visits and blood tests needed	* * * * *
Other cons:	* * * * *

What do you think about taking cyclophosphamide plus steroids? Check one

Willing to consider this treatment
Pros are more important to me than the Cons

Unsure

Not willing to consider this treatment
Cons are more important to me than the Pros

Step 3: Choose the role you want to have in choosing your treatment **Check ✓ one**

- I prefer to decide on my own after listening to the opinions of others
- I prefer to share the decision with: _____
- I prefer someone else to decide for me, namely: _____

Step 4: Identify what you need to help you make the decision

What I know	Do you know enough about your condition to make a choice?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unsure
	Do you know which options are available to you?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unsure
	Do you know the good points (pros) of each option?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unsure
	Do you know the bad points (cons) of each option?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unsure
What's important	Are you clear about which pros are most <i>important to you</i> ?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unsure
	Are you clear about which cons are most <i>important to you</i> ?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unsure
How others help	Do you have enough support from others to make a choice?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unsure
	Are you choosing without pressure from others?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unsure
	Do you have enough advice to make a choice?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unsure
How sure I feel	Are you clear about the best choice for you?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unsure
	Do you feel sure about what to choose?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unsure

If you answered No or Unsure to many of these questions, you should talk to your doctor.

Step 5: Plan the next steps

What do you need to do before you make this decision?

For example: talk to your doctor, read more about this treatment or other treatments for lupus kidney disease.

Step 6: Share the information on this form with your doctor

It will help your doctor understand what you think about this treatment.

Decisional Conflict Scale © A O'Connor 1993, Revised 1999.

Format based on the Ottawa Personal Decision Guide © 2000, A O'Connor, D Stacey, University of Ottawa, Ottawa Health Research Institute.