Cardiff & Vale (C&V) UHB Corporate Medicines Management Group (c MMG)

SHARED CARE

Drug: SIROLIMUS **Protocol number: CV 18**

Indication: RENAL, PANCREAS OR COMBINED RENAL PANCREAS TRANSPLANTATION IN ADULTS

General guidance

This protocol sets out details for the shared care of patients taking **sirolimus** and should be read in conjunction with the General Guidelines for Shared Care. Sharing of care requires communication between the specialist, GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. **The doctor who prescribes the medication legally assumes responsibility for the drug and the consequences of its use.** The prescriber has a duty to keep themselves informed about the medicines they prescribe, their appropriateness, effectiveness and cost. They should also keep up to date with the relevant guidance on the use of the medicines and on the management of the patient's condition.

Background

Drug therapy in transplantation is complicated and patients require regular assessment to monitor the progress of the transplant and to monitor for drug side effects. Anti-rejection agents must be continued for the duration of the life of the transplant but both the number of agents and doses prescribed are greater in the first year post surgery, especially in the first three months when the risk of acute rejection is greatest. After 12 months, the risk of acute rejection is lower but drugs are still required to prevent acute and, equally importantly, chronic rejection processes.

Most new transplant patients will be discharged from hospital on a combination of three anti-rejection drugs:

- Calcinuerin inhibitor (ciclosporin or tacrolimus)
- Anti-proliferative agent (azathioprine or mycophenolate mofetil)
- Corticosteroids (prednisolone)

Sirolimus is the first of a new class of anti-rejection agents called mTOR inhibitors. It suppresses T-cell proliferation through inhibitory actions on an intracellular regulatory kinase (mTOR) causing disruption to cell signalling, so is generally classed as an anti-proliferative agent.

Sirolimus can be prescribed as primary immunosuppression post transplant surgery in combination with ciclosporin (for 2 to 3 months only before gradual withdrawal of ciclosporin) and corticosteroids. Triple therapy regimens described above and those including sirolimus can produce significant benefits in terms of patient survival, reduction in the number of transplants lost through acute rejection and reduction in acute rejection episodes.

Patients also switch to sirolimus at a later date from the initial anti-rejection agents prescribed for them because of drug intolerance. In almost all circumstances this will be a switch from a calcinuerin inhibitor (ciclosporin or tacrolimus) because of nephrotoxicity. For many patients this side effect is a major factor in the progressive decline in the function of their kidney transplant (known as chronic allograft nephropathy). Sirolimus is relatively free of nephrotoxic effects and is classed as a "rescue therapy" in these situations.

Current practice at the transplant unit means that the vast majority of patients referred for shared care of sirolimus will be taking it as a "rescue therapy", with only a minority receiving it immediately post surgery.

A. Consultant responsibilities

1. When treatment is **initiated** send Shared Care request form with Shared Care Protocol to GP.
2. Baseline and continued monitoring of biochemical and haematological parameters, clinical parameters and therapeutic drug monitoring for sirolimus.
3. Initiate therapy following full discussion with the patient of benefits and risks.
4. Monitoring of clinical response, side effects and check any alteration in patient's medication.
5. When a GP positive response to SC has been received and patient has been stabilised (this can vary between 4 and 12 weeks post transplant) send a letter to GP "handing over" the Shared Care of the patient to the GP.
6. Advise female patients to consult with Transplant team if considering pregnancy.
7. Respond to any request from GP to review the patient due to adverse effects of therapy.
8. Advise the GP on continuing or stopping sirolimus therapy following medical review of the patient and associated drug therapy.
9. Notify GP if patient is failing to attend for appropriate monitoring and advise GP on appropriate action.

B. General practitioner responsibilities

1. Within one week of receipt return the completed Shared Care request form to indicate whether or not willing to undertake Shared Care.
2. Prescribe sirolimus as part of the shared care agreement.
3. Monitor the general health of the patient.
4. Seek advice from the consultant on any aspect of patient care which is of concern e.g. unexplained fever.
5. Report adverse effects of therapy to the consultant and the Medicines and Health Care products Regulatory Agency (MHRA).
6. Recommend that patient receives pneumococcal vaccination and annual influenza vaccination.
7. To act on advice provided by the Consultant if patient does not attend for appropriate monitoring.

C. Patient responsibilities

1. Consent to treatment with sirolimus.
2. Attend regular appointments with specialist centre and GP.
3. Report any side effects to the specialist or GP whilst taking sirolimus

Dosage Regimen

The initial dose (which would be started on day of transplant surgery) is usually a load of 6mg followed by 2mg as a single daily dose.

When transferring from other anti-rejection drugs the early stages of the switch must be managed carefully by the transplant unit to minimise the risks of over or under immunosuppression in this period. A loading dose is usually required and the initial maintenance dose is generally between 3 and 6mg as a single daily dose.

Sirolimus doses are always adjusted according to blood levels and clinical response. There is significant inter-patient variation in factors such as absorption and metabolism of sirolimus so the optimum dose will be determined individually for each patient.

Monitoring

<u>During treatment</u>

Regular measurement of trough (pre-dose) sirolimus levels, alongside a clinical assessment of the patient, are necessary to allow further dosage adjustments to be made. Target therapeutic levels when used as part of primary immunosuppression regimen:

- 4 to12ng/ml (when also taking ciclosporin)
- 12 to 20ng/ml (when ciclosporin has been withdrawn)
- The higher levels later on are necessary to respond to the reduced intensity of immunosuppression resulting from ciclosporin cessation

Target therapeutic levels when used as a “rescue therapy” are less clearly defined and will also depend on factors like concurrent anti-rejection drugs and risk of acute rejection. A range of 6 to 15ng/ml may be used to minimise the likelihood of sub-optimal immunosuppression and toxicity, respectively.

The frequency of these measurements will depend on the clinical situation as indicated by the consultant requesting shared care. For example, drug levels will be checked more frequently during periods when levels have become sub-therapeutic or toxic or when the patient is required to take a drug that interacts with sirolimus. Also, the role of therapeutic drug monitoring is less well established than it is for ciclosporin and tacrolimus. Sirolimus levels are checked less frequently and the precise relationship between blood levels and drug effects is not as clear, emphasising the need for a clinical assessment alongside a drug level.

Regular monitoring is crucial for the overall management of transplant patients. It will aid detection of side effects due to drugs such as sirolimus for which the following are routinely checked:

- Full blood count
- Creatinine and electrolytes
- Blood pressure
- Liver function tests
- Lipid profile

Each of these parameters will checked up to three times a week in the early post transplant phase. For a stable, long term patient this frequency reduces gradually but will always be a minimum of every 3 months.

Patients will be issued with a monitoring booklet to record results of these investigations.

When they attend transplant clinic, patients will be asked if any alterations have been made to their medication.

GPs should seek advice from Hospital Transplant team where the following blood test results (unrelated to sirolimus monitoring) are present.

WBC	$< 4x10^9$/L * and/or
Neutrophils count	$<1.5x\ 10^9$/L*
Platelets	$< 150 \times 10^9$/L*
Or 3 successive falls within the normal range	
AST/ALT	> 2-fold rise (from upper limit of reference range)

Adverse effects

The principal adverse effects are:

- Hypercholesterolaemia
- Hypertriglycerideaemia
- Bone marrow suppression (especially thrombocytopenia but also anaemia and leucopenia)
- Stomatitis
- Mouth ulcers
- Impaired wound healing

Other important side effects include:

- Hypertension
- Peripheral oedema
- Pneumonitis
- Lymphocele
- Rash

- Tachycardia
- Diarrhoea
- Hepatic dysfunction

Some sirolimus side effects are related to elevated blood levels.

Sirolimus is immunosuppressive and as such predisposes to infection. Chickenpox and measles in non-immune patients of all age groups can be particularly serious and such patients may require passive immunisation after contact. The hospital should be consulted.

Varicella-zoster infections must be treated with systemic antiviral therapy and herpes simplex infections may require topical or systemic antiviral therapy.

According to level of risk for the individual patient, prophylaxis may be required for between 3 and 6 months against cytomegalovirus (with valganciclovir), pneumocystis carinii pneumonia (with cotrimoxazole) or tuberculosis (with isoniazid).

Fever should be fully investigated with: -

- Blood culture
- Full blood count
- Urine culture
- Throat swab
- Full clinical examination to elicit the cause.

Fever may also be a sign of rejection.

Interactions

Sirolimus undergoes hepatic metabolism via cytochrome P450 enzyme systems. This is the same pathway that metabolises the calcinuerin inhibitors (ciclosporin and tacrolimus) so the overwhelming majority of interactions are common to both classes of anti-rejection agent. Many drugs can inhibit (for example macrolide antibacterials and azole antifungals) or induce (for example rifamycin antibacterials) the activity of these enzymes. This can lead to, respectively, elevated sirolimus levels (increasing risk of toxicity) or reduced sirolimus levels (increasing the risk of rejection).

Ciclosporin competes for metabolism with sirolimus in the gut wall and the liver and is metabolised preferentially so levels of sirolimus are increased. To overcome the interaction in the gut wall at time of drug absorption, patients are advised to take sirolimus 4 hours after their ciclosporin dose. When ciclosporin is withdrawn, sirolimus levels will fall and the dose will be escalated, especially when the need for higher drug levels at this stage is considered.

Grapefruit juice has constituents that inhibit sirolimus metabolism so patients are advised to avoid it.

If there are concerns about prescribing a drug for a transplant patient on sirolimus, the transplant unit should be contacted and the transplant doctor/nurse/pharmacist will be able to offer advice.

Special recommendations

Live vaccines must be avoided in all transplant patients.

There is an increased risk of skin cancer in transplant patients. They should be advised to take appropriate steps to protect themselves against the harmful effects of sunlight, to be vigilant for changes to their skin and to report these changes to the transplant unit.

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