Tacrolimus in the Management of Immune-Related Adverse Effects (IRAEs)

A guide for members on the prescribing and monitoring of tacrolimus when used in the management of IRAEs following of treatment with immune-checkpoint inhibitors.

British Oncology Pharmacy Association in Collaboration with The Immuno-Oncology Clinical Network

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1. Introduction

- Tacrolimus is a calcineurin inhibitor that has an immunosuppressant effect. Within its license it is used to prevent organ rejection in solid organ transplant patients. Off license it can be used as to treat multiple immune-related adverse events (irAEs) that can result from treatment with immune-checkpoint inhibitors. Either as a steroid sparing agent, or in steroid-refractory irAEs.

- Evidence exists for the use of tacrolimus in immune-related hepatitis and immune-related cholangitis, as per the ESMO guideline. In addition, there are case reports in a variety of other immune-related adverse events including colitis.

- This document is intended to be used as a monograph to provide prescribing and monitoring advice once the decision has been made to initiate tacrolimus. It is not a clinical guideline, but a consensus view of current use of tacrolimus when used for irAEs. It should be used in conjunction with any local policies/procedures/guidelines and should be approved for use according to the trust clinical governance processes.

2. Prescribing and Monitoring Advice

2.1 Contraindications

- Hypersensitivity to tacrolimus or other macrolides.
- Hypersensitivity to any of the excipients

2.2 Precautions

- Suspected lymphoproliferative disorder or unexplained anaemia, leukopenia or thrombocytopenia.
- Frail or elderly (Increased risk of infection)
- Chickenpox/shingles – stop tacrolimus if proven infection.
- Immunisations - Avoid live immunisations. Contact specialist for advice.
- Risk factors for QTc prolongation.

2.3 Pregnancy Advice

- Tacrolimus crosses the placenta so should only be used in pregnancy when there is no safer alternative, and the perceived benefit justifies the potential risk to the foetus.

2.4 Pre-treatment assessment

- Full blood count (FBC), urea and electrolytes (U&Es), liver function tests (LFTs)
- Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
- Baseline glucose
- ECG in patients with pre-existing heart disease

2.5 Pharmaceutical form

- Tacrolimus is available in two forms; immediate release (BD dosing) and prolonged release (OD dosing). Care is needed to ensure they are not inadvertently interchanged.
- It is recommended that immediate release capsules should be used first line, and prolonged release reserved for when there are concerns regarding adherence, or in cases of severe tremor.
- There are a variety of brands available for BD dosing including Prograf® and Adoport®, which are available in a number of different capsule strengths e.g. as 0.5mg, 1mg, & 5mg.
- Be vigilant of which brand being prescribed and how the dose is being made up.
- The capsules can be opened, and contents suspended in water if necessary.
- Tacrolimus is available in intravenous (IV) form. IV tacrolimus has complex dosing and is best avoided unless no viable alternative. Seek specialist advice if considering its use.

2.6 Dosage

- Typical doses are 0.10 - 0.20 mg/kg/day orally administered in two divided doses (e.g. morning and evening) using immediate release capsules.
- Typically, 2mg BD if <60kg, and 3mg BD if ≥60kg.
- Only consider use of prolonged release preparation at initiation if there are concerns with adherence.
- Dose adjustments should be made according to both clinical effect and therapeutic drug levels (see monitoring advice).

2.7 Therapeutic Drug Monitoring

- Therapeutic drug monitoring (TDM) is always used with tacrolimus in its licensed indication due to its narrow therapeutic index and variable pharmacokinetics between patients.
- The place of TDM for dose adjustment in the management of irAEs is less well understood with a lack of evidence base, and recommendations are extrapolated from the transplant literature, expert opinion and clinical experience of physicians who manage patients with autoimmune diseases.
- It is recommended to use TDM during treatment initiation. However, it is also important to adjust doses based on clinical response e.g. ALT levels in hepatitis.
- When TDM is used, the aim is a for a therapeutic trough target of between 5-8ng/mL balancing with the risk of nephrotoxicity and immunosuppression.
- Levels should be taken immediately prior to the morning dose; 12 hours post the evening dose.
- In cases where clinical efficacy is not seen within this range consider dosing to a higher range of 8-10ng/mL
- Once level taken, tacrolimus dose to be given immediately after but if a clinical response is needed quickly then level **must** be reviewed prior to the subsequent dose.
- If a clinical response is seen, despite levels below the target range, it may not be necessary to increase the tacrolimus dose. However, if clinical response not obtained then increase the tacrolimus dose by 0.5-1 mg/day until therapeutic levels are achieved.
- During initiation if the patient is an inpatient, it is advised to do daily tacrolimus levels. If the patient is well enough to be managed as an outpatient, in combination with steroids, then twice weekly TDM is advised.
- A level should be rechecked if a patient switches from BD to OD dosing, or changes brand.
- Once levels are stable and clinical response obtained, levels can be done less frequently. For example every 2-4 weeks at 3 months and every 4-6 weeks from 4 months.
- Contact hepatology if additional advice is needed on dose adjustments, due to extensive experience with the use of tacrolimus.

2.8 Other monitoring

- Creatinine – tacrolimus is not renally cleared, but it is common for it to cause a deterioration in renal function; close monitoring of creatinine is advised.
- FBC
- ALT and/or AST
- Albumin
- ECG in high-risk patients e.g. cardiac myopathy & risk of QT prolongation

Blood Test Results	**Advice**
WBC < 3.5 x 10^9/L	Withhold until discussed with specialist team
Neutrophils < 2.0 x 10^9 /L	Withhold until discussed with specialist team
Platelets < 150 x 10^9 /L	Withhold until discussed with specialist team
Unexplained reduction in albumin	Discuss with specialist team
Creatinine increase >30% over 12 months and/or calculated GFR	Withhold until discussed with specialist team
Lipids	Discuss abnormal result with specialist team – may be appropriate so start statin therapy
> 2-fold rise in AST, ALT (from upper limit of reference range)	Withhold until discussed with specialist team
Symptoms	
Unexplained rash	Withhold until discussed with specialist team
Abnormal bruising or bleeding	Withhold until FBC results available & discuss with specialist team
Severe sore throat	Withhold until FBC results available & discuss with specialist team

2.9 Adverse effects

- The table below outlines the broad range of adverse effects that patients can experience.
- The most commonly seen in the clinical setting include hypertension, renal dysfunction, headache and tremor.
- This is not an exhaustive list. See SmPC for further details.

System	**Adverse Effects**
Blood and lymphatic system disorders	Anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analysis abnormal
Metabolism and nutrition disorders	Hyperglycaemia, Diabetes Mellitus, electrolyte disturbances, reduced appetite, hyperlipidaemia

Psychiatric disorders	Insomnia, anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders
Nervous system disorders	Tremor, headache, seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders
Eye disorders	vision blurred, photophobia, eye disorders
Ear and labyrinth disorders	Tinnitus
Cardiac disorders	ischaemic coronary artery disorders, tachycardia
Vascular disorders	Hypertension, haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders
Respiratory, thoracic and mediastinal disorders	dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations
Gastrointestinal disorders	diarrhoea, nausea, gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms
Hepatobiliary disorders	cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis
Skin	Pruritis, rash, alopecia, acne, sweating increased
Musculoskeletal and connective tissue disorders	arthralgia, muscle spasms, pain in extremity, back pain
Renal and urinary disorders	renal impairment, renal failure, renal failure acute, oliguria, renal tubular necrosis, nephropathy toxic, urinary abnormalities, bladder and urethral symptoms
Investigations	liver function tests abnormal, blood alkaline phosphatase increased, weight increased

2.10 Drug interactions

- Tacrolimus is a substrate for CYP3A4 enzymes. Therefore, concomitant medications that inhibit or induce these enzymes should be avoided where possible.
- In addition, due to the risk of renal toxicity there is a risk of additive toxicity with other nephrotoxic drugs, so these should also be avoided.

- The tables below list the most common interactions but is not exhaustive. The SmPC and other drug interactions resources should be further consulted.

Drug	**Interaction**
Pomelo, Pomegranate and Grapefruit juice	Increase in Tacrolimus concentration
Live vaccines	Avoid. Increased risk of infections
Aminoglycosides	Increase risk of nephrotoxicity.
Amiodarone, Dronedarone	Increase in Tacrolimus concentration
Apalutamide, Enzalutamide	Reduction in Tacrolimus concentration
Aprepitant, Netupitant	Increase in Tacrolimus concentration
Atazanavir, Duranavir, Fosamprenavir, Letermovir, Lopinavir, Maribavir, Ritonavir	Increase in Tacrolimus concentration
Baricitinib, Filgotonib,	Increase of immunosuppressive effects
Berotralstat, Cobicistat, Pitolisant	Increase in Tacrolimus concentration
Bosentan	Decrease in concentration of both drugs
Cannabidiol	Increase in Tacrolimus concentration
Carbamazepine , Fosphenytoin, Phenobarbital, Phenytoin	Reduction in Tacrolimus concentration
Ceritinib, Crizotinib	Increase in Tacrolimus concentration
Chloramphenicol	Increase in Tacrolimus concentration
Ciclosporin	Increase in Tacrolimus and ciclosporin concentration
Clarithromycin, Erythromycin, Tigecycline	Increase in Tacrolimus concentration
Corticosteroids	Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels.
Diltiazem, Nircadipine, Verapamil, Nifedpine	Increase in Tacrolimus concentration
Fluconazole, Isavuconazole, Itraconazole, Ketoconazole, Miconazole, Posaconazole, Voriconazole	Increase in Tacrolimus concentration
Idelasib, Imatinib, Nilotinib	Increase in Tacrolimus concentration
Lumacaftor	Reduction in Tacrolimus concentration
Mifamurtide	Reduced efficacy of Mifamurtide. Contraindicated.
Non-steroidal anti-inflammatory drugs	Risk of nephrotoxicity; diclofenac is to be avoided, but ibuprofen and naproxen can be used with caution.
Primidone	Reduction in Tacrolimus concentration
Ranolazine	Increase in Tacrolimus concentration
Rifampicin	Reduction in Tacrolimus concentration; increase risk of nephrotoxicity

Sirolimus	Reduction in Tacrolimus concentration and increase in Sirolimus concentration
St John's wort	Reduction in Tacrolimus concentration
Tofacitinib	Increase in exposure to Tofacitinib

Advice to patients

- Capsules should be taken immediately following removal from the packaging. Patients should be advised not to swallow the desiccant.
- Capsules should be taken on an empty stomach or at least 1 hour before or 2 hours after a meal, to achieve maximal absorption.
- When attending for drug levels, this should be done in the morning before the morning dose, and the morning dose taken after blood test.
- Tacrolimus can affect their kidney function and so they should be advised to stay well hydrated.
- Contact their acute oncology team for advice if they experience fever, unexplained rash, abnormal bruising/bleeding or a severe sore throat.
- There are several significant drug interactions. Patients should be advised to avoid grapefruit juice, ibuprofen, and diclofenac. They should confirm with their oncology team before any new medicines are started, including those they buy over-the-counter. They should be told to avoid herbal remedies whilst taking tacrolimus.
- An example patient information leaflet is available in Appendix 1

3. Appendix 1 Example Patient Information Leaflet

What is Tacrolimus?

Tacrolimus is a drug used to supress the immune system. It is most used in patients who have had a liver or kidney transplant to prevent them rejecting their new organ.

It has also been found to be useful for the side effects that can occur when patients are given immunotherapy to treat cancer. In this case, the immune system has become active against one part of the body (e.g. the liver), and tacrolimus supresses the immune system to prevent damage to that area of your body.

The dose is worked out on your body weight. The dose may be adjusted depending on the drug levels in your blood. There are lots of different versions of tacrolimus. Usually, you will be given a brand that is to be taken twice a day, although some people are switched to once a day. Always confirm with the team looking after you, or your pharmacist if you are unsure which you have.

How do I take Tacrolimus?

Always refer to the label on your box for up to date dosing instructions. For twice a day dosing, take approximately 12 hours apart e.g. 10am and 10pm.

It should be taken on an empty stomach. You should not eat anything 1 hour before and 2 hours after you have taken it.

Capsules should be taken immediately following removal from the packaging. Lots of brands come with a desiccant in the packaging which you must not swallow.

Tacrolimus should not be taken with grapefruit juice as it interferes with the way the drug works.

Drug level monitoring.

The team looking after you will tell you when you need to have the tacrolimus level in your blood checked, to make sure the level in your bloods is right for you. When this happens, you should not take your morning dose, but bring it with you to take after you have had your bloods test. This is to ensure that the blood sample is taken approximately 12 hours after the last dose.

How long will I need to take Tacrolimus for?

Every patient is different, and how long you need treatment with tacrolimus for will depend on how well controlled the immunotherapy side effect is. In the majority of cases, you will only need to take it for a few months. However, there are some patients who will need to remain on tacrolimus longer term.

Does Tacrolimus have any side-effects?

There are several possible side effects that you may notice, although many people do not experience any of these. Always read the information leaflet provided in the box.

Side effects include:

- Tremor or pins and needles in the hands or feet
- Tacrolimus may affect the breakdown of glucose by the body. This makes your blood sugar too high and, in some patients, causes permanent diabetes.
- Raised blood cholesterol
- Poor appetite or feeling sick

- Constipation or trapped wind
- Headache
- Insomnia (difficulty in sleeping), vivid dreams/ nightmares/ hallucinations
- Hair loss
- Increased risk of infection: if you develop 'flu-like' symptoms, cough, sore throat, or a high temperature contact your oncology team immediately.
- Eye disorders: report any changes in your eyesight or appearance of your eyes as you will need prompt evaluation.
- Avoid excessive exposure to UV light including sunlight. Wear *at least* factor 30 sunscreen with a high UVA star rating, long sleeve clothing and wide brimmed hats. Avoid direct sun exposure between 11am - 3pm.

If you encounter someone with chickenpox or shingles, or if you develop either of these, you need to contact your doctor immediately.

It is important to tell your doctor of any side effects or unusual symptoms that you are experiencing. These may indicate that your blood concentrations of tacrolimus are too high, and the dose may need to be changed.

Staying well hydrated will help to prevent some of these side effects.

Can I still be vaccinated?

Some vaccines contain a live version of the virus. These are called live vaccines. You cannot have a live vaccine whilst you are on tacrolimus.

Please talk to your doctor if you are not sure about this.

Is it safe to be in the sun?

Limit the amount of time you spend in the sunlight and avoid exposure to ultraviolet light such as tanning machines. Wear protective clothing and use a sunscreen with a high sun protective factor (SPF).

Is it safe to become pregnant while I am taking Tacrolimus?

You may have already had these conversations with your oncology team before starting immunotherapy. It is important that you do not plan a pregnancy if you are on tacrolimus and should use effective contraception if sexually active.

Can I take other medicines whilst I am taking Tacrolimus?

Tacrolimus can interact with a lot of other medication. When you are started on tacrolimus it is important to let the team prescribing it for you know of all other medicines you are taking.

It is advised that you do not take ibuprofen, diclofenac or grapefruit. Avoid herbal medication whilst on Tacrolimus.

You should always check with your oncology team or pharmacist if you are started on any new medicines, including anything you may buy over the counter.

Supply of Tacrolimus

You must not stop taking tacrolimus unless advised to do so by your hospital team. It will be prescribed from the hospital, and it is important you make sure you don't run out of capsules.

Who can I contact for further information?

If you have any queries about your tacrolimus, the best people to speak to are the oncology team who you are under, the team of specialists who have prescribed the tacrolimus for you or an oncology pharmacist.

4. References

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6. Document control

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