Abatacept in the Management of Immune-Related Adverse Effects (irAEs)

A guide for members on the prescribing and monitoring of Abatacept when used in the management of irAEs caused by treatment with immune-checkpoint inhibitors.

It should be noted that this use is considered off-label use; relevant governance processes within each organisation should be followed to ensure the risks associated with this are mitigated.

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

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Contents

1. Introduction

- Abatacept is a fusion protein combining the extracellular domain of cytotoxic T-lymphocyte-associated-antigen-4 (CTLA-4) and a modified portion of human immunoglobulin G1 (IgG1). As abatacept has the extracellular domain of CTLA-4 it 'acts as CTLA-4' and binds to the CD80/86 present on the antigen presenting cell (APC). This prevents CD80/86 on the APC from binding to CD28 which is present on the T-cell therefore inhibiting the costimulatory pathway. Abatacept could be considered to have an opposite effect to ipilimumab.

- Abatacept is licenced, in combination with methotrexate, for treatment resistant rheumatoid arthritis, treatment resistant psoriatic arthritis and polyarticular juvenile idiopathic arthritis. Off licence there is evidence for its use to treat steroid refractory immune related myocarditis alone or in combination with other agents, namely ruxolitinib.

- The evidence for abatacept consists mainly of case reports and small case series. Both ESMO and ASCO recommend the use of abatacept in steroid refractory myocarditis as a second line immunomodulator after mycophenolate or tocilizumab.

- This document is intended to be used as a monograph to provide prescribing and monitoring advice once the decision has been made to initiate abatacept. It is not a clinical guideline, but a consensus view of current use of abatacept 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 abatacept.
- Hypersensitivity to any of the excipients.
- Severe and uncontrolled infections.

2.2 Precautions

- Immunisations - Avoid live immunisations concurrently or within 3 months after abatacept. Contact specialist for advice.
- Serious infections including sepsis and pneumonia, which have resulted in fatalities have been reported with abatacept. This is especially important as patients who have IO myocarditis will often be on high dose corticosteroids and other immunosuppressants which increases the risk of infection when abatacept is administered.
- There have been reports of tuberculosis (TB) in patients who have received abatacept and therefore patients MUST be screened for latent TB prior to administration. (e.g. QuantiFERON-TB Gold Test)
- Abatacept is considered a moderate risk for hepatitis B reactivation so may require prophylaxis if evidence of previous infection. If active infection this would be a relative contraindication for treatment, although it may be appropriate to initiate treatment with appropriate treatment.
- Maltose containing injectable products can interfere with the readings of blood glucose monitors that use test strips with glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ). On the day of the infusion, GDH-PQQ test strips can falsely elevated results. It is recommended to use methods that do not react with maltose, such as those based on glucose dehydrogenase nicotine adenine dinucleotide (GDH-NAD), glucose oxidase, or glucose hexokinase test methods.

- Abatacept contains 8.625 mg sodium per 250mg vial. For 4x 250mg vials the total sodium content is 34.5 mg. This is 1.7% of the WHO recommended maximum sodium intake of 2g. This might be significant in a patient on a sodium-controlled diet.

2.3 Pregnancy Advice

- Women of childbearing potential must use effective contraception during treatment and up to 14 weeks after the last dose of abatacept
- Adequate data does not exist in the use of abatacept in pregnant women.
- Preclinical data in embryo foetal development studies no undesirable effects were observed at doses up to a 29-fold a human 10mg/kg dose based upon AUC. Similarly in development studies on rats in the pre- and post-natal setting limited changes in immune function were noted at 11-fold higher than human 10mg/kg dose based upon AUC.
- Abatacept may cross the placenta into the serum of infants born to women treated with abatacept therefore these infants may be at increased risk of infection.

2.4 Pre-treatment assessment for steroid-resistant immune-related myocarditis

- If the troponin does not reduce significantly (>50% reduction from peak) and/or AV block, ventricular arrhythmias, or left ventricular dysfunction persist despite 3 days of i.v. methylprednisolone plus cardiac treatments, then steroid-resistant immune-related myocarditis is confirmed.
- Admission to ICU (level 3), treatment with i.v. methylprednisolone, and optimal CV treatment including mechanical support (when indicated) is recommended for patients with ICI-associated fulminant myocarditis.
- There is a lack of data to recommend a specific second-line immunosuppression regimen and MDT discussion is recommended.
- Patients with fulminant ICI-associated myocarditis, complicated by haemodynamic and/or electrical instability, require admission to the intensive care unit (ICU) and cardiogenic shock should be managed according to the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF.
- QuantiFERON-TB Gold Test to confirm the presence of active or latent tuberculosis
- Hepatitis Surface Antigen and Hepatitis B Core Total Antibody
- Cardiac troponin levels e.g. troponin T or troponin I (Troponin I is more cardiac specific than troponin T, therefore troponin I can help distinguish myositis from myocarditis as troponin T is raised in myositis)
- Electrocardiogram
- Transthoracic echocardiogram
- BNP or N-terminal pro-B-type natriuretic peptide (NT-pro-BNP)

Investigations used to confirm myocarditis may include:

- Cardiac magnetic resonance scans with T1 and T2 mapping, T2-weighted short tau inversion recovery
- Cardiac 68Ga-DOTATOC scan
- PET -FDG-CT scan
- Endomyocardial biopsy

2.5 Pharmaceutical form

- Abatacept- ORENCIA®- 250 mg powder for concentrate for solution for intravenous infusion
- There are other ORENCIA® preparations licenced for subcutaneous injection and are therefore not relevant to this indication

2.6 Dosage

- It is still unclear what the most effective dose is, and it is unclear which agent should be used for myocarditis after the failure of corticosteroids.
- The ASCO guideline recommends a dose of 500mg intravenously every 2 weeks for 5 doses. The ESMO guidelines do recommend abatacept but do not recommend a dose.
- Abatacept 10mg/kg (using actual bodyweight) rounded to the nearest whole 250mg vial has been used in various case series.
- One schedule being investigated in the ACHLYS study is a 3-dose schedule with a dose on Day 1, Day 5 and Day 14 and various doses are being studied. Another schedule being investigated in the ATRIUM trial is 10mg/kg on day 1 , day 2, day 14 and then another dose on day 28.
- In a case series from Salem et al. some patients with severe myocarditis received 20mg/kg combined with ruxolitinib and this modelled receptor occupancy in the subjects.
- No dose reductions are required for renal or hepatic impairment, but it has not been formally studied in either of these populations.

2.7 Method of administration

- Abatacept should be reconstituted according to the information in the summary of characteristics and be added to a 100ml bag of sodium chloride 0.9%
- The intravenous infusion should be administered over 30minutes via an infusion set combined with a sterile, non-pyrogenic, low-protein-binding filter (pore size of 0.2 to 1.2 µm)
- No routine use of pre-medications to prevent hypersensitivity is required.
- The rate of acute infusion related reactions in studies have ranged > 0.1% and ≤ 1% of patients treated with abatacept.

2.8 Is there therapeutic Drug Monitoring?

- No therapeutic drug monitoring is required for abatacept

2.9 Other monitoring

Troponin T	Would expect a reduction of 50% of troponin from peak to demonstrate response
Troponin I (value more cardiac specific)	Would expect a reduction of 50% of troponin from peak to demonstrate response
BNP or NT-pro-BNP	Would expect a reduction in BNP or NT-pro-BNP as evidence of response.
Electrocardiogram continuous measurement usually required	Assess for new heart block and tachyarrthymias
Transthoracic echocardiogram	To track an improvement in ejection fraction

2.10 Adverse effects

- These are the most common adverse effects.
- This is not an exhaustive list. See SmPC for further details.

System	Adverse Effects
Infections and infestations	Upper respiratory tract infection (including tracheitis, nasopharyngitis, and sinusitis), lower respiratory tract infection (including bronchitis), urinary tract infection, herpes infections (including herpes simplex, oral herpes, and herpes zoster), pneumonia, influenza.
Nervous system disorders	Headache, dizziness
Vascular disorders	Hypertension, blood pressure increased
Respiratory, thoracic and mediastinal disorders	Cough
Gastrointestinal disorders	Abdominal pain, diarrhoea, nausea, dyspepsia, mouth ulceration, aphthous stomatitis, vomiting
Hepatobiliary disorders	Liver function test abnormal (including transaminases increased)
Skin and subcutaneous tissue disorders	Rash (including dermatitis)
General disorders and administration site conditions	Fatigue, asthenia

2.11 Drug interactions

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

Drug	Interaction
Adalimumab	Increases risk of infections and serious infections
Anakinra	Increases risk of infections and serious infections
Certolizumab pegol	Increase the risk of neutropenia and serious infections
Etanercept	Increases risk of infections and serious infections
Filgotinib	Increase the risk of immunosuppression
Golimumab	Increases risk of infections and serious infections
Infliximab	Increased risk of infections and serious infections
Live vaccines	Avoid. Increased risk of infections
Rozanolixizumab	Monitor. Might decrease the concentration of abatacept

2.12 Advice to patients

No specific advice to patients having abatacept.

3. Appendix 1 Example Patient Information Leaflet

What is Abatacept?

Abatacept is an antibody treatment used to suppress the immune system. It is most commonly used to treat rheumatoid arthritis which has not responded to initial treatment.

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

The dose is worked out on your body weight or may be a fixed dose; it is not certain what the correct dose to administer of this drug is to treat heart inflammation (myocarditis).

How do I take Abatacept?

It is administered as a 30-minute intravenous infusion (into a vein) which is repeated at intervals.

How long will I have Abatacept treatment for?

Different schedules exist for the treatment of steroid refractory myocarditis. You might have three doses across a two-week period. Currently it is not clear what the best dosing schedule is, to treat myocarditis.

Does Abatacept have any side-effects?

Side effects include:

- Being at increased risk of infections in all parts of the lungs which could include pneumonia, viral infections such as influenza amongst others,
- Headache and dizziness,
- Rise in blood pressure,
- Cough,
- Pain in your abdomen,
- Diarrhoea,
- Nausea,
- Mouth ulcers,
- Vomiting,
- Blood tests that check your liver function being abnormal,
- Rash and inflammation of the skin,
- Feeling tired (fatigue).

Allergy like reactions can occur when abatacept is being administered. The symptoms of these reactions include low blood pressure, nausea, wheezing and difficulty breathing, flushing, throat tightness, chills, skin and rash (urticaria). This reaction is usually an emergency which needs to be managed urgently.

Can I still be vaccinated?

Some vaccines contain a live form of the virus. These are called live vaccines, and you cannot have a live vaccine whilst you are on abatacept or for 3 months after.

If you have an inactive vaccine, abatacept may impair your immune response to the vaccine and therefore make it less effective.

For more information, please discuss this with your doctor.

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

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 abatacept and should use effective contraception if sexually active.

Can I take other medicines whilst I am taking Abatacept?

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 Abatacept

It will be prescribed from the hospital.

Who can I contact for further information?

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

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5. Acknowledgements

BOPA Immunotherapy Specialist Advisory Group

6. Document control

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Authors / Editors version 1.0	Simon Jenkinson Lead Pharmacist Cancer Services, Royal Free London NHS Foundation Trust Bethan Mortley, Advanced Cancer Pharmacist, Swansea Bay University Healthboard Stuart Evans, Principal Pharmacisy Cancer Services, Swansea Bay University Health Board Alice Tew, Consultant Pharmacist, University Hospital Birmingham NHS Foundation Trust. Kate Young, Consultant Medical Oncologist Renal, Skin Cancers and Acute Oncology Deputy Divisional Medical Director The Royal Marsden NHS Foundation Trust		
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Contact details	sjenkinson@nhs.net