

Managing irAEs with checkpoint inhibitors

This is the lay version of the EULAR 'points to consider' for the diagnosis and management of rheumatic immune-related side effects in people taking checkpoint inhibitors for cancer. The original publication can be downloaded from the EULAR website: www.eular.org.

Kostine M, et al. EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors. *Ann Rheum Dis* 2021;80:36–48.
[doi:10.1136/annrheumdis-2020-217139](https://doi.org/10.1136/annrheumdis-2020-217139)

Introduction

EULAR recommendations give advice to doctors, nurses and patients about the best way to treat and manage diseases. EULAR has written new 'points to consider' on how to diagnose and manage rheumatic immune-related side effects in people taking a type of cancer drug called a checkpoint inhibitor.

Doctors, nurses, other health professionals and patients worked together to develop this advice. The patients in the team ensured that the patient point of view was included.

What do we already know?

Checkpoint inhibitors act on the immune system to treat several types of cancer. This group of drugs includes ipilimumab, nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab and durvalumab.

About 10% of people who take a checkpoint inhibitor drug to treat a cancer develop musculoskeletal side effects called *immune-related adverse events* (shorted to irAEs).

EULAR has written a set of 'points to consider' on how rheumatic irAEs should be diagnosed and managed. These aim to help oncologists and rheumatologists work together to treat people who develop these side effects. At the moment there is a very low level of evidence on this subject, so it is not possible to develop full recommendations.

What do the points say?

In total, there are 4 overarching principles and 10 points to consider. The principles highlight that these rheumatic and musculoskeletal irAEs are common in people taking checkpoint inhibitors, and should be managed on a shared-decision basis between patients, their treating oncologist, and the rheumatology team. Rheumatologists should work to assist the oncologist in differential diagnosis, and help to relieve symptoms to enable patients to maintain their cancer immunotherapy.

Each point is based on the best current knowledge and studies of scientific evidence or expert opinion. The more stars a point has the stronger the evidence is. However, even recommendations with limited scientific evidence may be important, because the experts may still have a strong opinion and the evidence may be lagging behind.

One star (*) means it is a recommendation with limited scientific evidence.

Two stars (**) means it is a recommendation with some scientific evidence.

Three stars (***) means it is a recommendation with quite a lot of scientific evidence.

Four stars (****) means it is a recommendation supported with a lot of scientific evidence.

- **Rheumatologists should be aware of the wide spectrum of rheumatic immune-related adverse events that often do not fulfil traditional criteria of rheumatic diseases.***

There is a lot of variation in the types of irAEs that people get from checkpoint inhibitors. These can include arthritis and joint pain, myositis, dry mouth, skin thickening, fever, fatigue, etc. Rheumatologists should be aware of the possible symptoms that can mimic rheumatic diseases.

- **Oncologists should consult rheumatologists quickly when rheumatic symptoms are suspected due to immunotherapy, and rheumatologists should provide access for these patients.***

If people taking checkpoint inhibitors develop rheumatic irAEs, their treating oncologist should quickly refer them to a rheumatologist, ideally before trying any steroid treatment. Rheumatologists should see these patients quickly as they are best-placed to try low-dose or steroid-sparing treatments.

- **Some side effects of the cancer itself or unrelated rheumatic diseases might look like immune-related events. Clinical evidence, laboratory tests, imaging and biopsies should be collected to search for inflammation and exclude other diseases.***

Checkpoint inhibitors are often used in people with advanced cancer, and so new rheumatic or musculoskeletal symptoms may not always be irAEs. The oncology team should collect clinical evidence to rule out cancer progression. It is important that this is done quickly to ensure the correct treatment can be given. Then, the rheumatologist should collect evidence of inflammation (on joints, on muscles, on vessels, etc...) either by clinical evidence, or blood tests and imaging, and if required with biopsies.

- **If other treatments do not work, steroids can be considered for symptoms that look like immune-related rheumatic or connective tissue diseases.***

If treatment with painkillers or non-steroidal anti-inflammatory drugs does not work to control your symptoms, you may be offered glucocorticoids (steroids). This will depend on your particular set of symptoms, but steroids injections or tablets can be useful for arthritis or joint pain. Once your irAE symptoms have improved, the steroid should be reduced to the lowest dose needed to maintain control. This is because steroids used for a long time or at a high dose can cause side effects or may alter how your tumour responds to treatment.

- **csDMARD should be considered in people with insufficient response to glucocorticoids or those requiring glucocorticoid-sparing.***

If steroids do not work to control your symptoms – or if they only work for you at a high dose (more than 10 mg per day) – then you may be offered a conventional synthetic disease-modifying antirheumatic drug instead (often shortened to csDMARD). These types of drugs include methotrexate, hydroxychloroquine or sulfasalazine.

- **bDMARDs can be considered for people with severe rheumatic and connective tissue disease-like immune-related adverse events or those with insufficient response to csDMARDs.***

People experiencing severe rheumatic and systemic irAEs, or those with an insufficient response to csDMARDs can try a biologic (also called a bDMARD). For people with symptoms of inflammatory arthritis, the preferred options are TNF or IL-6 inhibitors.

- **The decision to stop or to continue cancer immunotherapy should be made with the patient, based on side effect severity, the tumour response and duration, and the treatment plan.***

At the moment there is no agreement about whether people with irAEs should stay on the checkpoint inhibitor. This might vary depending on your country or treating team, but you should be involved in the

discussions and decision-making.

- **Myositis may be a severe condition, and stopping cancer immunotherapy needs to be discussed. If there are life-threatening symptoms, other treatment options can be used instead.***

Myositis is inflammation in a person's muscles, causing weakness and pain. Myositis can also affect the muscles of the heart, which can potentially be fatal. If myositis is suspected, it may be necessary to stop the checkpoint inhibitor. People who have life-threatening symptoms such as dysphagia, dysarthria, dysphonia, dyspnoea or myocarditis can be treated with high-dose glucocorticoids, intravenous immunoglobulin (IVIg) and/or plasma exchange.

- **Cancer immunotherapy can be used in people who have a pre-existing autoimmune rheumatic disease, while keeping their immunosuppressive treatment for the rheumatic disease at the lowest dose possible.***

People with pre-existing inflammatory or autoimmune diseases can take checkpoint inhibitors for cancer, but they and their treating team should be aware that they may experience disease flares. In most cases, these flares can be managed with steroids.

- **There is no need to test for autoantibodies before starting cancer immunotherapy, but these should be checked if there are rheumatic, musculoskeletal or systemic symptoms.***

Autoantibodies are not always present in people with irAEs, so there is no need to test everyone before they start treatment with a checkpoint inhibitor. However, it can be useful as part of a complete rheumatology assessment if you have unexplained rheumatic, musculoskeletal or systemic symptoms.

Summary

Overall, these points to consider provide the basis of a EULAR consensus in a new and rapidly expanding field. Early consultation and strong collaboration between the referring oncologist, the treating rheumatologist, other organ specialists and the patient are all required for optimal management.

Recommendations with just one or two stars are based mainly on expert opinion and may not be backed up sufficiently yet by studies. These may be as important as those with three or four stars.

If you have any questions or concerns about your disease or your medication, you should speak to a health professional involved in your care.