

Checkpoint inhibitors and arthritis: seeking balance between victories and defeats

Eventually, we heard the French proverb “*dans la médecine comme dans l’amour, ni jamais, ni toujours*” suggesting that medicine is unpredictable. The introduction of new therapeutic interventions in clinical practice accompanies this rule, arising both certainties and doubts, until experiences are shared to generate a conduit guide. However, just like any guide, medical guidelines should work as compasses, not as anchors, because real-life medicine constantly exposes physicians to new and unfamiliar situations, replete with previously unheard-of and unweighted variables.

The introduction of immune checkpoint inhibitors (ICIs) in the treatment of cancer is an example of this situation. Despite these drugs are one of the greatest therapeutic advances of medicine in the last decades, positive points emerge and also negative ones, providing a cascade of new knowledge, including rheumatic immune-related adverse event (irAE) induced by ICI.^{1 2} We read with great interest a manuscript written by Chan and Bass in this journal reporting a case of polymyalgia rheumatica (PMR) induced by ICI therapy that was partially treated with a MEK 1/2 inhibitor, proposing a possible correlation between the MEK/ERK pathway and PMR.¹ We emphasise that this was only allowed after the fortuity irAE associated with ICI therapy, coupled with the acumen of Chan and Bass to identify this possible correlation.

In the last 2 years, countless publications have flooded the journals with case series addressing the rheumatic irAE associated with the ICI. In February 2018, a practical guideline about the management of those irAEs was published in the *Journal of Clinical Oncology*.³ This guideline brought a breath to those professionals who longed for a specific orientation regarding the management of all irAEs. Interestingly, the guideline separated the rheumatic manifestations into inflammatory arthritis, polymyalgia rheumatic-like syndrome and myositis, as well as in three symptom grade system (mild, moderate and severe).³ The recommendations are illustrated in a table of that article wisely warning that “all recommendations are expert consensus based, with benefits outweighing harms and with moderate strength of recommendations”.³

We do not have the intention to solve the numerous questions that arose after the recognition of this entity, even though scientific evidence is still lacking so far. However we would like to score four ‘practical topics’ that still should be answered.

1) IN THE SO-CALLED “MILD CASES” OF ARTHRITIS ASSOCIATED WITH ICI, SHOULD ONCOLOGISTS ACTUALLY EXPECT REFRACTORINESS FROM THE CORTICOSTEROID THERAPY TO REFER TO THE RHEUMATOLOGIST?

We suggest that there are four reasons indicating that an earlier referral to the rheumatologist should be preferred: (1) the distinction between an inflammatory arthritis and a PMR syndrome may not be simple for the non-rheumatologist⁴; (2) classic inflammatory arthritis and PMR usually have different prognostic features as well as different management on rheumatology practice⁴; (3) these conditions may persist even after discontinuation of ICI therapy²; and (4) even if remote, there is a possibility that the articular manifestation has no correlation with ICI therapy, but with the neoplasm itself or another variable not previously considered. Thus, we see no reason to wait for specific situations (eg, refractory to corticoid) to referral to rheumatology.

2) IN THE SO-CALLED “MODERATE AND SEVERE CASES” OF RHEUMATIC IRAE, SHOULD WE ADVISE THE ONCOLOGIST TO HOLD OR NOT TO HOLD THE ICI THERAPY?

Daniel Kahneman is a psychologist who, interestingly, won the Nobel Prize in Economic Sciences. His book *Thinking Fast and Slow* comments about human psychological reactions based on hope to gain and fear to lose.⁵ He stated that usually people are willing to take a risk to prevent the loss of something, but are not prone to take a risk for an uncertain gain. In other words, it seems that for most people, the pain of loss is greater than the pleasure of winning. This also applies to our patients, and so we ask: is the ‘pain’ of losing the therapeutic effect of ICI greater or less than the pain of rheumatic symptoms?

Thus, although the articular pain may greatly impact the patient’s quality of life, knowing that they can be handled satisfactorily with disease-modifying antirheumatic drugs (DMARDs), while maintaining the ICI therapy, would not this be a good alternative? This question brings us to the third point.

3) IS THERE ANY PROBLEM TO CONCOMITANT USE OF DMARD AND ICI THERAPY?

This questioning arose after we noticed the guideline insistence on the use of symptomatic drugs, especially prednisone, delaying the introduction of DMARDs. The interface between oncological patients and rheumatic disease is by no means a new situation.^{6 7} Some colleagues may be thinking: “but the use of checkpoint inhibitors is a new situation; I will not risk using DMARDs in these cases”. It is a fair reluctance. This is why recent publications come to help us to shape our approach. Approximately 30% of patients with pre-existing rheumatic disease have experienced flares of their prior disorder in association with treatment using ICI for malignancy.^{8 9} In those cases, should we stop ICI therapy or should we stop the DMARD and add prednisone? Although this question seems rhetorical, fortunately, we may offer a third option. Methotrexate (MTX), leflunomide, hydroxychloroquine and sulfasalazine have been used concurrently with ICI therapy in some cases without any known damage so far. One consideration with these therapies, however, is their slow onset of action. So, in patients with limited life expectancy, they may fail to achieve optimal effect quickly enough to improve the impairments in quality of life.^{10–12}

Even that, despite oncologists may be reluctant in the concomitant use of DMARD and ICI therapy, we do not see, until now, any contraindication of this combination, especially if it is a non-biologic DMARD. Although the use of MTX in oncology is associated with worrying adverse events, it is justified by the high doses practised by them. In rheumatology, the use of MTX, as well as other non-biologic DMARDs like hydroxychloroquine and leflunomide, is extremely safe at the doses practised, including in concomitance with immunobiological therapies, sponsoring improvement of symptoms, interruption of disease progression and early weaning of the corticosteroid.^{13 14} However, although there are reports of use of biologic-DMARD therapy in some cases (eg, infliximab, tocilizumab and etanercept), due to the molecular peculiarity involved with those drugs, we believe that more caution is necessary when considering their use concomitant with ICI therapy, especially tocilizumab because of the overlapping risk of intestinal perforation, and abatacept, because it directly opposes the mechanism of ICIs.^{2 3}

4) DO WE HAVE ANY GOOD NEWS FOR THE PATIENT WHO HAS MUSCULOSKELETAL irAE SECONDARY TO ICI THERAPY?

As Eugen Weber said, “bad times to live are good to learn”.¹⁴ This kind of thinking is very useful, especially when we are talking about cancer with our patients. Many of them think everything is lost and, when the ICI therapy arrives to soften their desires, an irAE appear. The manuscript of Kostine *et al* evaluated the prevalence and type of rheumatic irAEs in patients receiving ICI, as well as the correlation with tumour response.¹⁵ Fortunately, they noted that tumour response was significantly higher in patients who experienced rheumatic irAEs. Although our tendency to find that checkpoint immunotherapy is bad for rheumatic diseases,¹⁶ time may show us the opposite. Talking about this possibility with our patients does not mean giving them false hope, but rather showing that a coin has two sides.

FINAL CONSIDERATIONS

The balance that must be pursued should be of a controlled cancer disease with the patient maintaining quality of life without adding side effects resulting from antirheumatic drugs, including those associated with prolonged use of corticosteroid. It is just another battle in which we must seek the benefits of victory by avoiding the griefs of defeats.

Of course the decision of whether the ICI therapy should be held or not needs to be made on an individual basis, but it is important for the rheumatologist to keep in mind that our focus should be to maintain the oncologist’s comfortability with the ICI therapy as well as chase away the patient’s fear of losing the benefit of cancer treatment while maintaining them with their quality of life. It is a situation that a good doctor–patient relationship is essential and especially a good rheumatologist–oncologist relationship is mandatory.

Management of these cases is the time when the art overlaps with science. There are no masters of truth. Articles from Kostine *et al*¹⁵ and Chan and Bass¹ are showing us that ‘a coin has two sides’, and that this theme still hangs over a penumbra. Just like in life, we have to have the balance to keep moving, valuing the victories and managing the defeats.

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Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

Author note All authors confirm that the manuscript has been read and approved by all of them.

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To cite Moura CA, Moura CG. *Ann Rheum Dis* Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2018-213866

Received 1 June 2018

Accepted 8 June 2018

Ann Rheum Dis 2018;0:1–2. doi:10.1136/annrheumdis-2018-213866

REFERENCES

- Chan KK, Bass AR. Checkpoint inhibitor-induced polymyalgia rheumatica controlled by cobimetinib, a MEK 1/2 inhibitor. *Ann Rheum Dis* 2018. doi: 10.1136/annrheumdis-2018-213672. [Epub ahead of print].
- Belkhir R, Burel SL, Dunogean L, *et al*. Rheumatoid arthritis and polymyalgia rheumatica occurring after immune checkpoint inhibitor treatment. *Ann Rheum Dis* 2017;76:1747–50.
- Brahmer JR, Lacchetti C, Schneider BJ, *et al*. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2018;36.
- Cutolo M, Cimmino MA, Sulli A. Polymyalgia rheumatica vs late-onset rheumatoid arthritis. *Rheumatology* 2009;48:93–5.
- Kahneman D. *Thinking fast and slow*: Editora Farrar, Straux and Giroux, 2011.
- Naschitz JE, Rosner I. Musculoskeletal syndromes associated with malignancy (excluding hypertrophic osteoarthropathy). *Curr Opin Rheumatol* 2008;20:100–5.
- Johnson DB, Sullivan RJ, Ott PA, *et al*. Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. *JAMA Oncol* 2016;2:234–40.
- Abdel-Wahab N, Shah M, Lopez-Olivo MA, *et al*. Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review. *Ann Intern Med* 2018;168:121.
- Chan MM, Kefford RF, Carlino M, *et al*. Arthritis and tenosynovitis associated with the anti-PD1 antibody pembrolizumab in metastatic melanoma. *J Immunother* 2015;38:37–9.
- Cappelli LC, Gutierrez AK, Baer AN, *et al*. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. *Ann Rheum Dis* 2017;76:43–50.
- Calabrese C, Kirchner E, Kontzias K, *et al*. Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity. *RMD Open* 2017;3:e000412.
- Cappelli LC, Shah AA, Bingham CO. Immune-Related Adverse Effects of Cancer Immunotherapy- Implications for Rheumatology. *Rheum Dis Clin North Am* 2017;43:65–78.
- Bello AE, Perkins EL, Jay R, *et al*. Recommendations for optimizing methotrexate treatment for patients with rheumatoid arthritis. *Open Access Rheumatol* 2017;9:67–79.
- Weber – Eugen. *The Hollow Years: France in the 1930s*. Nova York: W.W. Norton, 1994:5.
- Kostine M, Rouxel L, Barnetche T, *et al*. Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer—clinical aspects and relationship with tumour response: a single-centre prospective cohort study. *Ann Rheum Dis* 2018;77:393–8.
- Calabrese L, Velcheti V. Checkpoint immunotherapy: good for cancer therapy, bad for rheumatic diseases. *Ann Rheum Dis* 2017;76:1–3.