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THERAPY

Rheumatic symptoms associated with immune checkpoint inhibition

Rheumatic immune-related adverse events occur in some patients with cancer being treated with immune checkpoint inhibitors (ICIs). A new study by Kostine *et al.* highlights the wide variety of rheumatic immune-related adverse events that occur in such patients and suggests that the occurrence of these adverse events might predict a favourable response to ICI therapy.

Immune checkpoints are negative regulators of the immune response that promote tolerance and prevent excessive self-reactivity. However, tumour cells can use these immune checkpoints to evade the immune system. Inhibition of these checkpoints has been used as a revolutionary new therapy for many cancers. The ICIs currently approved for clinical use target either the cytotoxic T lymphocyte protein 4 (CTLA4) pathway or the programmed cell death protein 1 (PD1) pathway. However, immune checkpoint inhibition is also associated with various immune-related adverse events.

Kostine *et al.* sought to evaluate the prevalence of rheumatic immune-related adverse events in patients with cancer receiving ICI therapy. From a cohort of 524 such patients, 35 (6.6%) were referred to rheumatology services with any type of rheumatic symptoms; some patients had inflammatory arthritis (3.8%) that mimicked either rheumatoid arthritis (RA), polymyalgia rheumatica (PMR) or psoriatic arthritis, whereas others had non-inflammatory musculoskeletal conditions (2.8%). "While our study confirms that RA and PMR-like patterns are the most frequent rheumatic immune-related adverse events, the description of other clinical entities such as PMR-like patterns without increased levels of C-reactive protein, as well as non-inflammatory immune-related adverse events, is new and noteworthy for practicing rheumatologists," states corresponding author Marie Kostine.

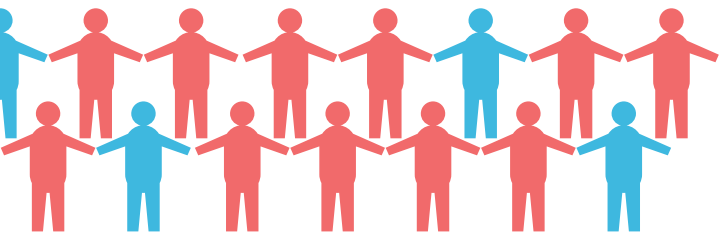
> "the occurrence of rheumatic immune-related adverse events could be a marker for an efficient and durable antitumour response"

For the majority of patients with inflammatory arthritis, low to moderate doses of glucocorticoids were sufficient to treat their musculoskeletal symptoms, with only two patients also requiring methotrexate therapy. By contrast, non-inflammatory musculoskeletal symptoms were effectively managed with NSAIDs, analgesics and/or physiotherapy. ICI treatment was continued in all but one patient, indicating that these adverse events can be effectively managed without the need to modify ICI treatment.

Of note, a higher proportion of patients with cancer who developed rheumatic immune-related adverse events were responsive to ICI treatment than those patients who did not develop rheumatic immune-related adverse events (85.7% vs 35.3%; $P < 0.0001$). These results are in line with the hypothesis that the occurrence of rheumatic immune-related adverse events could be a marker for an efficient and durable antitumour response. Furthermore, the majority of patients who presented with rheumatic immune-related adverse events were receiving anti-PD1 or anti-PD1 ligand 1 treatment, rather than anti-CTLA4 treatment, indicating that the onset of inflammatory arthritis might be related to the use of specific ICIs. Thierry Schaeverbeke, a co-author of the study, explains that the patients in this study will continue to be followed up to answer questions such as the long-term effect of these immunosuppressive strategies, to help to develop treatment algorithms and to investigate the phases of preclinical disease.

"This work emphasizes the need for a broad education among the rheumatologic community on rheumatic immune-related adverse events, the need for an international consensus on how to manage these complications, and especially the need for prospective studies to search for predictive biomarkers and to elucidate the basic underlying immunopathogenesis of these complications, of which our understanding is woefully incomplete," remarks Leonard Calabrese, who was not involved in the study.

Jessica McHugh



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ORIGINAL ARTICLE Kostine, M. *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.* http://dx.doi.org/10.1136/annrheumdis-2017-212257 (2017)
FURTHER READING van der Vlist, M. *et al.* Immune checkpoints and rheumatic diseases: what can cancer immunotherapy teach us? *Nat. Rev. Rheumatol.* **12**, 593–604 (2016)