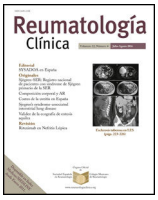
Reumatol Clin. 2019;15(5):249–251

Sociedad Española de Reumatología - Colegio Mexicano de Reumatología

Reumatología Clínica

www.reumatologiaclinica.org



Editorial

Immunotherapy, cancer and rheumatic diseases☆

Inmunoterapia, cáncer y enfermedades reumatológicas

Francisco Javier Nóvoa Medina,[a,*] Delvys Rodríguez Abreu[b]

[a] *Sección de Reumatología, Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Gran Canaria, Spain*
[b] *Servicio de Oncología, Complejo Hospitalario Universitario Insular Materno-Infantil de Gran Canaria, Gran Canaria, Spain*

Treatment in oncology has experienced great advances in recent years. Immunotherapy and its ability to block immune checkpoints has become standard treatment for several types of tumours.

The inhibition of immune checkpoints aimed against protein 4 of cytotoxic T-lymphocyte (CTLA-4: ipilimumab and tremelimumab), and protein 1 of programmed cellular death (PD-1: nivolumab and pembrolizumab) and its ligand (PD-L1: atezolizumab and durvalumab), have significantly improved the survival of non-microcytic lung cancers (NMLC), metastatic melanomas, Hodgkin lymphomas and renal and urothelial carcinomas. The benefits of immunotherapy also extend into other fields, such as the ease with which the hospital pharmacy may prepare them thanks to the use of standard doses, a shorter infusion time without administration of premedication and the lower frequency of side effects with depletion of neutrophils.

However, immunotherapy is responsible for the so-called immune-related adverse events (IRAE) where rheumatic diseases appear to play a major role. Immunotherapy produces an overstimulation of the immune system which could arise from a cross-over reaction between tumour antigens and healthy tissues and lead to the adverse effect.[1]

Basic aspects of immunotherapy

Modern immunotherapy is a type of biological therapy which stimulates the immune system to combat cancer, among other things. It has existed, per se, for centuries. The development of the first vaccine against smallpox in the 18th century was an example of immunotherapy. However, several decades had to pass for it to gain the prominence it currently has.

The idea of using the immune system to fight tumours was new in the 1980s, but doctor William B. Coley used it for the first time at the end of the 19th century to treat patients with sarcoma. However, Coley's experiments did not convince the medical circles of the time and it was not until 1957 that immunotherapy began to take off in the cancer treatment.[2] Since then, different types of immunotherapy have been used, with monoclonal antibodies being the most novel immune-check-points inhibitors and the latest to be marketed. There are many clinical trials under development for this type of molecule.

Ipilimumab (m-antibody against -CTLA-4) was approved in 2011 by the Food and Drug Agency and the European Medication Agency for the treatment of metastatic melanoma. Later, in 2014, they approved two monoclonal anti PD-1 antibodies (nivolumab, pembrolizumab) which had demonstrated their efficacy in patients with melanoma, NMLC, renal cell carcinoma and Hodgkin's lymphomas. Then, in 2016 and 2018 PDL-1 monoclonal antibodies were approved: atezolizumab for urothelial carcinoma and NMLC and durvalumab for NMLC.

The different immune-check-points inhibitors presented different mechanisms of action and activation, being interrelated to one another to maintain an immunological harmony. Together with CTLA-4 it essentially acts as an early step in the immune response. It is believe that PD-1 acts as an inhibitor of the T lymphocyte in later stages in peripheral tissues and that it could have a role in the maintaining of auto tolerance. The different functions and mechanisms of action of these immune control points are reflected in the different side effects they generate.

The CTLA-4 inhibitors tend to cause more severe and frequent side effects (they involve gastrointestinal type colitis, cutaneous side effects and endocrine hypophysitis type side effects) whilst the PD-1 and PDL-1 inhibitors are more frequently associated with systemic autoimmune disease, pneumonitis or thyroiditis.[3] Combined or double block therapy with anti-PD-1 and anti-CTLA-4 inhibitors achieves further improvements in clinical response compared with immunotherapy, and also an increased risk of IRAE.[3,4]

It should also be highlighted that the safety profile of the immunotherapy varies depending on the type of tumour. IRAE usually appear in the first 3–6 months of their administration and in some cases are signs of good treatment response. The majority of

☆ Please cite this article as: Nóvoa Medina FJ, Rodríguez Abreu D. Inmunoterapia, cáncer y enfermedades reumatológicas. Reumatol Clin. 2019;15:249–251.

* Corresponding author.
E-mail address: fnovmed@hotmail.es (F.J. Nóvoa Medina).

studies indicate that prolonged treatment with immunotherapy does not result in an accumulated increased incidence of IRAE.[3,4]

Immunotherapy, cancer and rheumatology

Hyperstimulation of T lymphocytes leads to reactivity in healthy tissues. It is unknown what the exact pathophysiological mechanism is which leads to this but it is thought that mechanisms relating to T lymphocytes, the production of auto antibodies and the induction of proinflammatory cytokines. (IL-17) could be involved.[4]

The most common rheumatic IRAE are inflammatory arthritis and rheumatic polymyalgia. They also described a dry syndrome and inflammatory myopathy type connective pathologies, giant cell arthritis type vasculitis, systemic or lupos erythematosus or sarcoidosis. At present there is no definition or tool to communicate haematological IRAE in clinical trials and there is concern that they may be underdiagnosed.[5,6]

Published series

One of the most active groups has been that of Capelli et al., from the John Hopkins hospital. In their series[7] of 30 patients with inflammatory arthritis they reported that the clinical symptoms of the arthritis could have been related to the type of immunotherapy used, in such a way that the patients treated with PD-1/PDL-1 inhibitors tended to present with involvement of the minor joints as the first point of location and to present the arthritis as the only IRAE, whilst the patients with dual therapy presented with higher involvement of the major joints and higher acute phase reactants.

Cases were also described of connective pathologies of lupus nephritis, systemic sclerosis, sarcoidosis and vasculitis.[6]

There are series[8,9] in which prior to immunotherapy the presence of serological markers were observed (antipeptide cyrulinade antibodies, antinuclear antibodies, anti-Ro antibodies) without any clinical significance, and that after immunotherapy they developed diseases related to these, which were rheumatoid arthritis types or Sjögren syndrome type. However, there are no studies which establish whether the presence of them could be a predictor to the development of the disease like IRAE.

Another issue to probe is what happens in patients with rheumatic diseases who begin immunotherapy. Calabrese et al.[1] reported of a patients with psoriatic arthritis who had to restart apremilast due to the worsening of the skin condition. In the series by Richter et al.[10] it was observed that only a minority of patients presented with an outbreak of their underlying disease.

Assessment of rheumatic IRAE

From the pathophysiological viewpoint, it would be interesting to discover, among other issues, whether the IRAE act or do not act in a similar way to autoimmune rheumatic diseases and whether antibodies play a major role in their physiology and diagnosis. Something which has not been investigated is that certain conditions, such as sero-negative arthritis, inflammatory myopathies and rheumatic polymyalgias present in many patients as paraneoplasic symptoms and are precisely the conditions which present most as IRAE.

In clinical practice and based on the recommendations published by different work groups[6,11] and scientific societies[12,13] if there is a suspicion of IRAE, the request for serological markers and/or other routine complementary tests in the management of the rheumatologic diseases would help to made an early and appropriate diagnostic.

With regard to treatment, algorithms have already been established[12,13] for the treatment of arthritis type rheumatologic IRAE, inflammatory myopathies and rheumatic polymyalgia. According to these, treatment has to be scaled, taking into account that, depending on the grading-severity of the IRAE, treatment differs, and may even include a recommendation to use biological therapy and the suspension of immunotherapy. The established waiting time for switching from one therapeutic step to another must be between 4–6 weeks.

The use of immunosuppressants for the treatment of IRAE has been contested by some authors since it may interfere in the efficacy of immunotherapy.[14] However, retrospective studies exist which show that the results of the patients who were treated with immunosuppressant were no worse in terms of survival than those who did not receive them.[15]

The possible side effects of the immunosuppressants should also be taken into consideration and the preventative measures which are usually recommended (for example, screening tests for latent tuberculosis in patients who begin treatment with TNF-Alfa inhibitors, preventative osteoporosis treatment induced by corticoids, prophylaxis for the *Pneumocystis jirovecii* infection in patients who need it). We should highlight that they are patients who will not only receive immunosuppression by rheumatic IRAE but also who have received and may continue receiving immunotherapy, with the result that the risk of serious infection is therefore increasing.[15]

Conclusion

Studies published up until now show that there is a relationship between immunotherapy and rheumatic diseases, but they continue to give rise to many questions. Firstly, the real incidence of the rheumatic pathologies bearing in mind the possible underestimation of these due to the lack of standardization in diagnosis. Secondly, the therapeutic approach to be followed and the impact this has on the tumour and on the established rheumatic disease. Lastly, the concomitant effect of immunotherapy and immunosuppresion in patients with a history of previous rheumatic disease.

References

1. Calabrese C, Kirchner E, Kontzias K, Velcheti V, Calabrese LH. Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity. RMD Open. 2017;3:e000412.
2. Hoption Cann SA, van Netten C. Dr William Coley and tumour regression: a place in history or in the future. Postgrad Med J. 2003;79:80–672.
3. Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, et al. Immune-related adverse events with immune checkpoints blockade: a comprehensive review. Eur J Cancer. 2016;54:48–139.
4. Longo DL. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378:158–68.
5. Cappelli LC, Gutierrez AK, Bingham CO 3rd, Shah AA. Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: a systematic review of the literature. Arthritis Care Res (Hoboken). 2017;69:63–1751.
6. Capelli LC, Shah AA, Bingham CO III. Immune-related adverse effects of cancer immunotherapy implications for rheumatology. Rheum Dis Clin N Am. 2017;43:65–78.
7. Cappelli LC, Brahmer JR, Forde PM, Le DT, Lipson EJ, Naidoo J, et al. Clinical presentation of immune checkpoint inhibitor-induced inflammatory arthritis differs by immunotherapy regimen. Semin Arthritis Rheum. 2018;48:553–7.
8. Le Burel S, Champiat S, Routier E, Aspeslagh S, Albiges L, Szwebel TA, et al. Onset of connective tissue disease following anti-PD1/PD-L1 cancer immunotherapy. Ann Rheum Dis. 2018;3:468–70.
9. Belkhir R, Burel SL, Dunogeant L, Marabelle A, Hollebecque A, Besse B, et al. Rheumatoid arthritis and polymyalgia rheumatica occurring after immune checkpoint inhibitor treatment. Ann Rheum Dis. 2017;76:50–1747.
10. Richter MD, Pinkston O, Kottschade LA, Finnes HD, Markovic SN, Thanarajasingam U. Cancer immunotherapy in patients with preexisting rheumatic disease: the Mayo Clinic experience. Arthritis Rheumatol. 2018, http://dx.doi.org/10.1002/art.40397.
11. Naidoo J, Cappelli LC, Forde PM, Marrone KA, Lipson EJ, Hammers HJ. Inflammatory arthritis: a newly recognized adverse event of immune checkpoint blockade. Oncologist. 2017;22:627–30.
12. Brahmer J, Lacchetti C, Schneider B, Atkins MB, Brassil KJ, Caterino JM, 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;36:1714–68.
13. Puzanov I, Diab A, Abdallah K, Bingham CO III, Brogdon C, Dadu D, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5:1–28.
14. Horvat TZ, Adel NG, Dang TO, Momtaz P, Postor MA, Callahan MK, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. J Clin Oncol. 2015;33:8–3193.
15. Del Castillo M, Romero FA, Arguello E, Kyi C, Postow MA, Redelman-Sidi G. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. Clin Infect Dis. 2016;63:3–1490.