POS1341

TOCILIZUMAB FOR THE TREATMENT OF IMMUNE-RELATED ADVERSE EVENTS TO IMMUNE CHECKPOINT INHIBITORS: A CASE SERIES

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Background: Immune checkpoint inhibitors (ICI) are pharmacological agents effectively used in the treatment of several malignant tumors. The hyperactivation of the immune system induced by ICI may trigger an inflammatory involvement of healthy tissues, a phenomenon referred to as immune-related adverse event (irAE). No clinical trials are available to guide the management of irAEs. Observational data suggest tocilizumab might be effective in severe cases of irAEs, but data are scant. The possibility of continuing ICI treatment despite the development of irAE and the subsequent initiation of tocilizumab has never been evaluated.

Objectives: To evaluate the efficacy and safety of tocilizumab, as monotherapy or alongside the continuation of ICI treatment, in the management of irAEs.

Methods: We retrospectively identified patients who developed irAEs and were referred to our specialized Clinic between May 2018 and December 2020. Among these patients, we identified those who had been treated with tocilizumab and collected information about their oncologic history and outcome, ICI therapy and irAEs.

Results: Thirty-nine patients were referred to our outpatient Clinic following the development of irAEs. Five of them were treated with tocilizumab. Disease and demographic features are reported in Table 1. At irAEs onset all patients were treated with glucocorticoids. A steroid-sparing agent was started to permit an adequate prednisone tapering without the irAE relapsing. Before tocilizumab start, two patients were treated with methotrexate monotherapy, one with anakinra monotherapy, and one with methotrexate and anakinra combination therapy. A significant therapeutic effect was confirmed in all patients and no significant adverse reactions were reported. ICI therapy was permanently discontinued in two patients. In the other three cases, cancer immunotherapy was safely continued alongside tocilizumab without further irAEs occurring. Only one patient experienced tumor progression two years after ICI suspension and subsequently died despite the improvement of his myocardial inflammatory involvement.

Conclusion: In our cohort, tocilizumab proved to be an effective and safe therapy for the management of irAEs.

Our case series also supports the possibility of maintaining ICI while introducing tocilizumab for irAE treatment. This combined approach might represent a suitable therapeutic option to guarantee a significant anti-inflammatory activity without losing the oncologic response.

REFERENCES:

[1] Kostine M *et al*, Ann Rheum Dis, 2021;80:36-48.

Table 1. Clinical characteristics of patients who developed irAEs secondary to ICI therapy and who received tocilizumab.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at irAE onset (years)	69	52	72	57	75
Sex	Male	Male	Male	Female	Female
Neoplastic histology	NSCLC	NSCLC	NSCLC	NSCLC	Pleural mesothelioma
ICI treatment	Nivolumab	Nivolumab	Pembrolizumab	Pembrolizumab	Pembrolizumab
irAE	Myocarditis	Arthritis	Arthritis	Arthritis	Large vessel vasculitis
ICI discontinuation due to irAE	Yes	No	No	No	Yes
PDN initial dose (mg daily)	50	37.5	25	25	37.5
DMARD therapy	T16: ANK T20: TCZ T26: TCZ + MMF	T5: MTX T6: MTX + ANK T11: MTX + TCZ	T3: MTX T11: MTX + TCZ	T4: MTX T6: MTX + TCZ	T3: TCZ
irAE outcome	Improvement	Low disease activity	Low disease activity	Remission	Remission
Follow-up length (months)	50 10	47 25	57 2	25 5	26 8
Since oncologic diagnosis					
Since TCZ start					
Oncological outcome	Progressive disease and death	Complete response	Stable disease	Stable disease	Complete response

* Treatment chronology is referred to as a T followed by the number of months since irAE onset. ANK, anakinra; ICI, immune checkpoint inhibitor; irAE, immune-related adverse events; DMARD, disease modifying anti-rheumatic drug; MTX, methotrexate; NSCLC, non-small cell lung cancer; PDN, prednisone; TCZ, tocilizumab.

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POS1342

CHEMOPROPHYLAXIS IN LATENT TUBERCULOSIS ASSOCIATED WITH RHEUMATIC IMMUNE-MEDIATED DISEASES. STUDY OF 240 PATIENTS FROM A SINGLE UNIVERSITY HOSPITAL

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Background: Tuberculosis (TB) may be increased with biologic therapy (BT). Diagnosis and treatment of latent TB infection (LTBI) is the best strategy to prevent TB. In Rheumatic Immune-Mediated Diseases (R-IMID) and LTBI, chemoprophylaxis must be used before BT. The drugs more frequently used are Isoniazid (INH), Rifampicin (RIF) and Fluoroquinolones (FQ). These drugs may be associated with side-effects, especially hepatotoxicity.

Objectives: To assess, in a single University Hospital, a) used chemoprophylactic drugs and, b) adverse events with these drugs.

Methods: We included all consecutive patients in the last five years (2016-2020) with a diagnosis of R-IMID and a positive LTBI test (positive tuberculin skin test and/or interferon-γ-release assay), who received chemoprophylaxis prior to BT. Dose of chemoprophylactic drugs were a) INH (5 mg/kg/d, maximum, 300 mg; for 9 months with vitamin B6), b) RIF (10 mg/kg/d, maximum, 600 mg for 4 months) and c) FQ levofloxacin (500 mg/day for 9 months).

In all patients analytic controls that included liver enzymes were performed at the 1st and 3rd month and then at a variable time.

Results: 240 patients were analyzed (165 women/ 75 men), mean age of 56±11 years. The underlying R-IMID of patients receiving chemoprophylaxis were rheumatoid arthritis (n=74, 30.8%), axial spondyloarthritis (n=59, 24.6%), psoriatic arthritis (n=62, 25.8%), connectivopathies (n=17, 7.1%), vasculitis (n=12, 5%), sarcoidosis (n=2, 0.8%), Behçet's disease (n=1, 0.4%), inflammatory myopathies (n=1, 0.4%) and other (n=12, 5%).

At the onset of chemoprophylaxis they were taking: Prednisone in 61 patients (24 of them above 10 mg/day) and the following conventional DMARD, methotrexate (n=109, 45.4%), hydroxychloroquine (n=20, 8.3%), sulfasalazine (n=11, 4.6%), leflunomide (n=4, 1.7%) and azathioprine (n=2, 0.8%).

The first-line chemoprophylactic drug was INH in 232 (96.7%) patients and RIF in the remaining 8 (3.3%). Due to adverse events, second-line therapy was used in 18 (RIF, n=17 and Levofloxacin, n=1) patients previously treated with INH.

Adverse events were more frequent with INH, being observed in 55 patients (23.7%) out of 232. (Table 1 next page, Figure 1 below). By contrast, only 1 out of 25 (4%) receiving RIF presented an adverse event, which was hepatotoxicity, requiring suspension of RIF. No adverse events were described in the only patient receiving levofloxacin.

Figure 1. Liver enzyme elevation over baseline in patients in treatment with isoniazid.* Patients with higher liver enzyme elevation are included in the previous groups.

Conclusion: INH is the most used first-line treatment for LTBI. RIF was mainly used as second-line therapy if an adverse event with INH was observed. Treatment was generally well tolerated and most adverse events did not require the withdrawal of the treatment. Hepatotoxicity was the most frequent adverse event with INH and the most frequent cause of treatment withdrawal.