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Immunity in rheumatic disease

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IS IMMUNE CHECKPOINT INHIBITORS THERAPIES SAFE AND EFFECTIVE FOR PATIENTS WITH CANCER AND PREEXISTING AUTOIMMUNE DISEASE?

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Background: Immune checkpoint inhibitors (ICIs) are associated with frequent immune-related adverse events (irAEs). Most patients with preexisting autoimmune disease (PAD) have been universally excluded from clinical trials and ICIs are not recommended for patients with cancer and PAD due to the unknown safety. In this study, we aim to evaluate the safety and efficacy of ICIs in patients with PAD and cancer.

Objectives: Systematic searches were performed of PubMed, EMBASE, and the Cochrane library from inception through September 2019 for observational studies reporting safety and efficacy data among ICIs-treated patients with cancer and PAD. A random effects meta-analysis was performed to calculate pooled incidence rates of PAD flare, irAEs and response.

Methods: Systematical search of PubMed, EMBASE and Cochrane Library plus a hand search of conference proceedings were performed for observational studies that reported cancer incidence in patients with RA treated with biologics or tofacitinib with active comparator of conventional DMARDs (csDMARDs) or TPNF. The pooled relative risk (RR) and 95% confidence interval (CI) were calculated with fixed-effect and random-effect models.

Results: A total of 231 ICI-treated patients with PAD in 14 publications were finally identified. In the random effects meta-analysis, pooled incidence of PAD flare, de novo irAEs or both of any grade was 60% (95% CI 52%-68%). Viewed separately, there were 219 and 206 patients experiencing PAD exacerbation and de novo irAEs of any grade, yielding a pooled incidence of 35% (95% CI 29%-41%) and 33% (95% CI 24%-42%) respectively. Of these, most of flare and de novo irAEs were graded as mild (grade 1-2) (pooled proportion: 82%, 95%CI 72%-91%; 65%, 95% CI 54%-76%, respectively). Rheumatoid arthritis was associated with a trend toward higher flare occurrence compared with another individual PADs (RR=1.25-1.88). With respect to efficacy, 136 patients showed complete and partial response, corresponding to a pooled response rates of 30% (95% CI 22%-39%). There were no statistical differences between patients with and without immunosuppressive therapy at ICI start regarding flare (RR: 1.08, 95% CI 0.72-1.62), but a trend towards lower response rates was observed in patients with baseline immunosuppressants (RR: 0.58, 95% CI 0.26-1.33).

Conclusions: Immune toxicities are frequent in ICIs-treated patients with PAD but often mild and manageable without discontinuing therapy. Rheumatoid arthritis is associated with a trend toward more flares. ICI treatment are effective and not absolute contraindication in PAD patients, but close monitoring and multidisciplinary collaboration should be contemplated, especially for those concomitantly receiving immunosuppressant or having rheumatoid arthritis.

References:
Background: DR-Tph cells are newly identified pathogenic CD4+ helper T cells in rheumatoid arthritis (RA). Since Tph cells have been emerged quite recently, the characteristics of Tph cells as a biomarker of RA are not fully understood.

Objectives: The aim of the study is to evaluate how useful Tph cells in peripheral bloods are when compared to other immune cell subsets, and to clarify which Tph subset most accurately reflects the disease activity of RA.

Methods: The RA patients who visited our rheumatology department between January 2000 and February 2017, and met the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria were included. We first assessed correlation with 40 immune cell subsets and the disease activity of RA. Next, the proportions of these immune cells were compared between RA and healthy controls (HCs). We also investigated the immune cell subsets which reflected the time course change of the disease activity after the methotrexate (MTX) treatment. The study protocol was approved by the ethics committee at Keio University School of Medicine.

Results: Thirty-four seropositive RA, 12 seronegative RA and 34 HCs were included. The immune cell subsets which showed correlation with DAS28-ESR (r > 0.2 or r < -0.2) were activated CD4 T cells (r = 0.31), HLA-DR+Th1 cells (r = 0.20), HLA-DR+Th1-17 cells (r = 0.25), Th1-17 cells (r = 0.25), HLA-DR+Tph cells (r = 0.22), CD3+CD8+naïve T cells (r = 0.25), CD3+CD8+effector memory T2 cells (r = 0.26), plasma cells (r = 0.40) and CD14++CD16+intermediate monocyte (r = 0.23). The proportions of HLA-DR+Th1 cells (2.3% vs. 5.7%), HLA-DR+Th1-17 cells (0.7% vs. 2.2%), Th1-17 cells (1.7% vs. 2.0%), HLA-DR+Tph cells (0.02% vs. 0.1%), CD3+CD8+effector memory T cells (16.6% vs. 25.7%), plasma cells (0.04% vs. 0.17%) were statistically higher in the patients with RA compared to HCs. While the proportion of Tph cells showed weak correlation with DAS28-ESR (r = 0.18), that was extremely higher in RA (0.80% vs. 0.25%). Interestingly, when assessing the correlations with the disease activity in seropositive and seronegative RA separately, the proportions of Tph cells (r = 0.52) and HLA-DR+Tph cells (r = 0.50) were highly reflected in seropositive RA, but not in seronegative RA. Regarding the disease activity after the MTX treatment, the change of proportion of Tph cells between week 0 and 52 significantly reflected the change of DAS28-ESR (r = 0.75, p = 0.025), but not HLA-DR+Tph cells because of the non-specific reduction by the MTX treatment. Rather, HLA-DR-Tph cells significantly reflected the change of DAS28-ESR while receiving the MTX treatment (r = 0.76, p = 0.021).

Conclusion: Tph cells and HLA-DR+Tph cells highly reflected the disease activity of seropositive RA. However, after the treatment, the proportion of HLA-DR+Tph cells decreased independent from the disease activity, and that of HLA-DR+Tph cells more accurately reflected the change of the disease activity during the treatment.

References: