TOCILIZUMAB MAY INDUCE SECONDARY HYPOGAMMAGLOBULINAEMIA. A RETROSPECTIVE CASE SERIES OF 42 PATIENTS

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Background: Tocilizumab (TCZ) is a recombinant humanized, anti-human monoclonal antibody of the immunoglobulin G1 subclass directed against soluble membrane-bound interleukin 6 receptors (IL-6R) [1]. Interleukin-6 (IL-6) has a pleiotropic effect on inflammation, immune response, and hematopoiesis. When it was first identified, it was named as B-cell-stimulating factor 2 (BSF-2) according to its ability to induce immunoglobulin production in Epstein-Barr virus-transformed B-cell lines or in Staphylococcus aureus Cowan I-stimulated B cells [2-4]. Nowadays, it is known that IL-6 controls the survival, population expansion and maturation of B cells and plasmablasts. In that way, the regulation of Blimp-1 by STAT3 is linked to antibody secretion and is associated with long-lived plasma cells that produce large amounts of immunoglobulin. Furthermore, the ability of IL-6 to promote humoral immunity has been linked to its effects on follicular helper T cells where they promote B cell proliferation and immunoglobulin class switching [5].

Objectives: Hypogammaglobulinemia is a known complication of some immunosuppressive drugs, not previously described in patients who received therapy with monoclonal antibody against the IL-6R. We aimed to analyze the prevalence of hypogammaglobulinemia in our series of patients treated with tocilizumab after a carefully diagnostic workup which ruled out other causes and analyzed whether it is associated with a higher infection risk. We determined them in the blood analysis performed by usual clinical practice.

Methods: We conducted a retrospective review from 2010 to 2019 of forty-two patients affected with a rheumatic disease and treated with TCZ at our centre. In those patients in whom we had no record of immunoglobulin levels, we determined them in the blood analysis performed by usual clinical practice.

Results: 42 patients were identified, from whom 38 had rheumatoid arthritis. A 31% had immunoglobulin levels prior to starting treatment with TCZ but no one had hypogammaglobulinaemia. 2 patients were excluded due to their underlying disease could justify the IgG level abnormalities. During the treatment’s follow-up, we identified that a 30% of the patients (12/40) had hypogammaglobulinaemia. Of those patients in whom immunoglobulin levels had been determined prior to starting treatment with TCZ, a 36.3% of them (4/11) developed hypogammaglobulinaemia during the follow-up. From the series, we observed a statistical significance tendency (p=0.0057) for infection risk in those patients with hypogammaglobulinaemia in contrast to those with normal IgG level (41.5% vs 14.3%, respectively).

Conclusion: Secondary hypogammaglobulinaemia may occur in patients receiving anti-IL6 agents such as tocilizumab and this could be associated with an increased infection risk. The prevalence is not precisely known, in part because measurement of IgG prior to or during the treatment has not been a standard of care. No medical data have been previously disclosed about this possible adverse effect of anti-interleukin-6 agents. Nevertheless, ideally randomized trials are needed to assess this initial hypothesis.

References:

RISK OF MALIGNANCY WITH NON-TNF BIOLOGIC OR TOFACITINIB THERAPY IN RHEUMATOID ARTHRITIS: A META-ANALYSIS OF OBSERVATIONAL STUDIES

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Background: With an increasing usage of non-TNF biologics and tofacitinib, it is crucial to understand the comparative safety of these agents regarding malignancies risk.

Objectives: We aim to assess the risk of developing cancer in patients with RA exposed to non-TNF inhibitors (TNFi) biologics or tofacitinib therapy.

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 TNFi. The pooled relative risk (RR) and 95% confidence interval (CI) were calculated with fixed-effects or random-effects model.

Results: Of 2,819 identified articles, a total of 10 studies involving over 323,361 patients and 1,179,263 patient-years of follow-up were included. Pooled analysis showed there was no increased risk of developing cancer in general or specific cancer types in RA patients receiving treatment with rituximab (pooled RR 1.13, 95% CI 0.80-1.59), tocilizumab (pooled RR 0.96, 95% CI 0.83-1.11), or tofacitinib (pooled RR 0.97, 95% CI 0.66-1.43), compared with those receiving csDMARDs or TNFi. However, abatacept use in RA was associated with a slightly increased overall cancer risk (pooled RR 1.13, 95% CI 1.02-1.24) and non-melanoma skin cancer (pooled RR 1.26, 95% CI 1.09-1.45), relative to csDMARDs or TNFi.

Conclusion: Compared with csDMARDs or TNFi, there was no increased risk of malignancies among RA patients treated with non-TNF biologics or tofacitinib, with exception of abatacept associated with slightly increased total cancer and specific cancer types. Extended researches are required to confirm the findings in a real-world context.

References: