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Do tumor necrosis factor inhibitors increase cancer risk in patients with chronic immune-mediated inflammatory disorders?

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ABSTRACT

Inhibition of tumor necrosis factor (TNF) activity has profoundly changed the management of several immune-mediated inflammatory diseases with great benefit for patients. The application of TNF inhibitors (TNFi), however, also brings a new concern, malignancy. We performed a systemic review to collect the studies reporting cancer incidences and risks in TNFi users regardless of indications. TNFi were most frequently used in treating patients with rheumatoid arthritis (RA) and inflammatory bowel diseases (IBD). In RA patients without prior cancer history, the incidences of malignancies ranged from the lowest rate 0 per 1000 person-years in etanercept users regarding lymphoma to the highest rate 35.62 per 1000 person-years in adalimumab users on non-melanoma skin cancer (NMSC), while in those patients with prior cancer history, the recurrent incidences of malignancies ranged from the lowest rate 5.05 per 1000 person-years regarding melanoma to the highest rate 63.20 per 1000 person-years on basal cell carcinoma (BCC) in TNFi users. In IBD patients, incidences ranged from 0 per 1000 person-years in TNFi users on lymphoma to 34.0 per 1000 person-years in infliximab users on overall cancer. However, these incidence rates of overall cancer, lymphoma and melanoma were not higher in comparison with those patients who were not treated with TNFi. Compared to general population, incidences of lymphoma were elevated in RA patients and rates of NMSC were higher in patients with psoriasis, RA and IBD. In conclusion, cancer incidences vary across different studies, indications, cancer types and studies with different individual TNFi. Treatment with TNFi is not associated with increased malignant risks of overall cancer, lymphoma or melanoma. Results of NMSC risk were inconsistent among studies. A latest prospective registry study demonstrated a small increased risk of squamous cell cancer in RA patients treated with TNFi (one additional case for every 1600 years of treatment experience). Further prospective studies are needed to verify whether TNFi users have higher NMSC risk than non-TNFi users.

1. Introduction

Tumor necrosis factor (TNF), a pro-inflammatory cytokine, is mainly generated by macrophages, monocytes, and T-cells, and plays a crucial role in inflammatory response and innate immunity. Its receptors are TNF receptor type 1 (TNFR1) (also known as TNFR p55) expressed on the surface of almost all human cell types excluding erythrocytes, and TNFR2 (also called TNFR p75) expressed chiefly on immune and endothelial cells. After binding to the two different receptors, TNF induces variable biological effects [1]. However, excessive expression of TNF and its receptors in the regulation process of inflammatory response and immune reaction is implicated in the pathogenesis and development of immune-mediated inflammatory diseases. TNF was first identified as an upstream cytokine in the inflammatory cytokine cascade in rheumatoid arthritis (RA) and was the first cytokine identified as therapeutic target in the treatment of a number of inflammatory diseases [2–5].

Since 1998, five branded TNF inhibitors (TNFi) have been licensed for clinical use, namely, infliximab (IFX), etanercept (ETN), adalimumab (ADA), certolizumab pegol (CZP) and golimumab (GLM). Most recently, an IFX biosimilar is also approved by US Food and Drug Administration to market in the US. Outside US, ETN biosimilars have been prescribed for many years. IFX, ADA, CZP and GLM are monoclonal antibodies. IFX, the prototype TNFi, is a chimeric; ADA is a humanized, while GLM is a full human monoclonal antibody. Certolizumab pegol is a humanized, PEGylated

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Fab fragment of monoclonal antibody. Whereas, ETN is a fusion protein of soluble TNFR2 and human IgG1 Fc fragment. While all the monoclonal antibodies specifically bind to TNF, ETN binds to TNF and lymphotoxin. The clinical efficacy of all these TNFi is comparable.

Collectively, the indicated conditions for TNFi include RA, juvenile idiopathic arthritis (JIA), Crohn's disease (CD), ulcerative colitis (UC), ankylosing spondylitis (AS), psoriasis (PsO), psoriatic arthritis (PsA) and non-infective uveitis. Although TNFi are a highly effective therapy that has drastically improved the care of many patients with immune-mediated inflammatory diseases, the risk of adverse events has continued to be a source of worry for patients and their providers. In particular, the risk of malignancy has been a major source of concern and debate. With increased passage of time and more widespread use of these medications, more robust and longer term data are available regarding the incidence and risk of malignancy in patients using these drugs. In particular, analyses from TNFi registries provide data reflecting the situation in daily clinical practice. This review is performed in order to summarize these data and our understanding to date of the risk of malignancy associated with the use of TNFi therapy. Since IFX, ETN and ADA have been in use for longer durations, most of the studies are derived from these TNFi.

2. Methods

2.1. Literature search

We systematically searched the electronic databases of OVID Medline and OVID EMBASE (from January 1st, 2000 to February 28, 2016) using a combination search of MeSH terms and keywords. Our search terms were "tumor necrosis factor-alpha", "tumor necrosis factor alpha antibody", "adalimumab", "certolizumab pegol", "etanercept", "golimumab", "infliximab", "malignancy", "cancer", "neoplasm", "carcinoma", "cancer epidemiology", "prevalence rate" and "incidence rate". We limited search results to human.

2.2. Study selection criteria

We included the studies, containing original studies and studies used pooling analysis for data (i.e., meta-analysis), reported incident rates of overall malignancy, lymphoma, non-melanoma skin cancer (NMSC) and/or melanoma in TNFi users no matter what indications. TNFi should be ADA, CZP, ETN, GLM, IFX or the combination use of any these agents. The studies were excluded if they met any one of the following statements: not related to incident rates of malignancy; not correlated with TNFi therapy; could not acquire useful data; duplications (i.e., data from the same database for the same outcomes); conference abstracts, letters, narrative reviews and non-English publications.

2.3. Data extraction

We extracted the following information from included studies: first author, year of publication, country, treatment indications, data sources, patient number and duration of follow-up (median years) in TNFi group and control group; malignancy type, cancer cases, follow-up duration (patient-years) and crude incident rate (per 1000 patient-years) in TNFi group. We also collected the relative risk (RR), hazard ratio (HR), incidence rate ratio (IRR), odds ratio (OR) and/or standardized rate ratio (SIR) of TNFi in contrast with control group or general population.

If there were several studies from the same registry or database, we collected the longest follow-up results in a study and outcomes of the most recent report with the largest study population.

2.4. Data processing

Incident rates were collected according to the report of a study. If a study only presented cancer number and follow-up duration, incident rate would be calculated via cancer number divided by follow-up patient-years and then multiplied 1000, acquiring the unit per 1000 patient-years.

Relative risk and adjusted relative risk (aRR), hazard ratio and adjusted hazard ratio (aHR), incidence rate ratio (IRR) and standardized rate ratio (SIR) were acquired according to the reports of the eligible studies. RR, HR, IRR and SIR were reported for the comparisons of TNFi users to control group patients with the disease not treated with biologics or treated only with traditional disease-modifying anti-rheumatic drugs (DMARDs), and to general population.

3. Results

A total of 1900 studies were retrieved from databases. After selection, 53 studies [6–58] proved eligible. Additionally, 3 studies [59–61] were included through manual searching references and 3 recently published studies [62–64] were also added. Of the 59 studies, 41 were original studies (37 were cohort studies, data in two studies were from clinical trials' database and post marketing surveillance database, and the remaining two studies: one was the Rheumatoid Arthritis Prevention of Structural Damage (RAPID)1 trial and its open-label extension study, the other was open-label extension study of randomized controlled trial) and 18 were pooled analysis (11 were integrated studies from clinical trials, two collaborative studies from biologic registers and five were meta-analyses). Of all the included studies, 27 focused on RA, 11 focused on inflammatory bowel disease (IBD) including CD and UC, three on JIA, three on PsO, one on spondyloarthropathies (SpA), one on AS, and 13 on blended rheumatic conditions. The median follow-up duration ranged from 0.2 years to 6.8 years in TNFi group (from 0.2 years to 12.0 years in control group) in original studies. Of the 59 eligible studies, 22 studies were performed in USA, seven in Sweden, five in UK, four in China, three each in Belgium and Germany, two each in Denmark, Finland, France, Italy, the Netherlands and Canada, and one each in Australia, Japan, Spain (Supplementary Tables 1 and 2).

3.1. Cancer incidence and risk in RA patients in original studies

3.1.1. Cancer incidence and risk in RA patients without prior cancer history

In RA patients, cancer incidences varied among different studies, disease indication, TNFi, and cancer type, ranging from the lowest rate 0 per 1000 person-years in ETN users regarding lymphoma and overall cancer [19] to the highest rate 35.62 per 1000 person-years in ADA users on NMSC [59] (Table 1).

For RA patients using TNFi regardless of subtypes, the overall cancer incidences varied from 5.1 per 1000 person-years (44 cancer cases and 8558 person-years of follow-up) [23] to 13.8 per 1000 person-years (34 cases and 2465.3 person-years) [9]. Berghen et al. [9] and Pallavicini et al. [22] reported gender subgroup incident rates of overall higher malignancy incidence rates for males than females, with 21.79 and 25.82 respectively for males, and 11.24 and 5.23 respectively for females. With respect to lymphoma in RA patients on TNFi, the highest reported incidence rate was 3.12 per 1000 person-years [14] and the lowest report was 0.8 per 1000 person-years [16]. Askling et al. [7] and Pallavicini et al. [22] both reported higher lymphoma incidences in men (1.37 (9 cases in 6544 person-years) and 8.61 (3/348.57) respectively) than in women (0.83 (17/20436) and 0.58 (1/1702.08) respectively).

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