THE EFFECTS OF TUMOUR NECROSIS FACTOR INHIBITORS ON CARDIOVASCULAR RISK IN IMMUNE-MEDIATED INFLAMMATORY DISEASES

Ph.D. Thesis Booklet

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1. Introduction

1.1. What is the topic?

The focus of the research lies in the investigation of the effects of tumour necrosis factor inhibitors (TNFis) on cardiovascular (CV) risk in immune-mediated inflammatory diseases (IMIDs).

1.2. What is the problem to solve?

IMIDs, like rheumatoid arthritis (RA), psoriasis (PsO), psoriatic arthritis (PsA), or inflammatory bowel diseases (IBD), are chronic conditions associated with an increased risk of the appearance of different comorbidities compared to the general population, including the development of CV diseases. The adequate sequencing of the anti-inflammatory therapies can play a critical role in preventing CV events. The excess CV risk in IMIDs may partly stem from TNF-mediated pathways, which are involved in the pathogenesis of IMIDs and atherosclerosis. Accordingly, TNFis can be superior to conventional systemic non-biological (CSNB) treatments in reducing atherosclerosis-derived CV risk in IMIDs. However, currently TNFis are generally placed as only

second-line systemic therapies after the application of CSNBs. Furthermore, although growing evidence suggests TNFis lower the risk of atherosclerosis-driven events, these biologics are referred to as potential risk factors for developing heart failure (HF) in the IMID therapeutic guidelines. Conflicting literature and new data since the risk of HF associated with TNFis was identified warrant the review of the evidence.

1.3. What is the importance of the topic?

CV diseases, with the occurrence of severe CV events, significantly diminish the quality of life and lower the life expectancy of IMID patients. Besides that, due to their long-term and complex treatment requirements, the management of IMIDs places a considerable financial burden on healthcare systems worldwide.

1.4. What would be the impact of our research results?

The present two studies contribute to the broadening of the understanding of the effects of TNFis on CV risk, thus the development and revision of IMID treatment guidelines for patients with CV comorbidities. The

optimisation of the sequence of the anti-inflammatory therapies provides an opportunity to reduce CV risk and prevent CV events in IMID patients with high CV burden.

2. Objectives

2.1. Study I. - Investigating the effect of TNF inhibitors compared to conventional therapies on atherosclerotic CV events in IMIDs

In recent years, many studies have explored the CV risk-lowering effect of anti-inflammatory therapies, including CSNBs and biologics, among them TNFis. The common TNF-mediated pathways of IMIDs and atherosclerosis, as well as novel data, suggest the potential superiority of TNFis on atherosclerosis-driven CV events compared to CSNBs in IMIDs. The objective of Study I. was to investigate the risk of CV events with TNFis compared to CSNBs comprehensively in IMID patients.

2.2. Study II. - Investigating the effect of TNF inhibitors on the risk of heart failure in IMIDs

The current therapeutic guidelines warn of the possibility of the development of de novo HF with TNFis, recommend cautious use with milder disease, and contraindicate the use of TNFis in IMID patients with advanced HF. In Study II., our aim was to comprehensively collect and synthesise data, thus

investigating the risk of de novo and worsening pre-existing HF in TNFi-treated patients compared to non-TNFi-treated controls in IMID populations.

3. Methods

Two systematic reviews and random-effect meta-analyses were performed following the actual recommendations of the Cochrane Handbook for Systematic Reviews and Interventions. The study protocols were registered on PROSPERO with the identification numbers of CRD42022375491 (Study I.) and CRD42023451099 (Study II.).

For the systematic literature search, MEDLINE via PubMed, Cochrane Library (CENTRAL), and Embase databases were applied in Study I., and one further source, Web of Science, was involved additionally in Study II. In both studies, original journal articles reporting the findings of randomised controlled trials (RCTs) and observational, comparative interventional studies were eligible for inclusion.

3.1. Study I. - Investigating the effect of TNF inhibitors compared to conventional therapies on atherosclerotic CV events in IMIDs

Studies comparing TNFi-treated patients with CSNB-receiving groups were included. Atherosclerosis-

associated CV events were sorted into different groups based on their definitions, with the main outcomes comprising major adverse cardiovascular events (MACE), myocardial infarction (MI) and cerebrovascular events (CeVE). For the statistical analyses of the main outcomes, multivariate hazard ratios (HR) and incidence rate ratios (IRR), along with 95% confidence intervals (CIs), were applied.

3.2. Study II. - Investigating the effect of TNF inhibitors on the risk of heart failure in IMIDs

Studies were involved in the systematic review and meta-analysis comparing TNFi-receiving and non-receiving groups among IMID patients, with the evaluation of the outcome of HF. The reported outcomes were primarily classified as de novo and worsening of HF events. Data from RCTs and non-randomised observational studies were handled separately during the analyses. As a result of measures in the meta-analysis, risk ratios (RRs) and 95% CIs were used.

4. Results

4.1. Study I. - Investigating the effect of TNF inhibitors compared to conventional therapies on atherosclerotic CV events in IMIDs

Through the process of systematic search, a total of 8,724 hits were identified. Following the duplicate removal, the title and abstract, and full-text selections, 56 articles were eligible for inclusion.

Data derived from 29 studies, with almost 500,000 patients, could be included in the quantitative analysis.

The overall effect of the analysis of fully adjusted multivariate HRs with the outcome of MACE indicated a statistically significant reduction in the TNFi-treated group compared to the CSNB controls (HR=0.74, CI: 0.58-0.95) in the IMID populations of RA, PsO and PsA. Significant risk reduction could also be observed in the subgroup analysis of RA patients. In the analysis of pooling IRRs for the evaluation of the risk of MACE, a comparable, significant risk-lowering effect was shown in the TNFi group compared to CSNBs (IRR=0.77, CI 0.67-

0.88). In the subgroup analyses of RA, PsO and PsA patients, the significant decreases in TNFi groups remained (IRR=0.68, CI 0.46-1.00 and IRR=0.79, CI 0.64-0.98, respectively).

The risk of CeVE was assessed with the involvement of data from RA, PsO, PsA, and IBD patients. In the analysis of fully adjusted multivariate HRs, an almost 30% lower, statistically significant reduced risk was shown in TNFi-treated patients compared to CSNB controls (HR=0.7, CI 0.55-0.91). Similar pooled overall effect indicating the superior effect of TNFis versus CSNBs could be observed with the synthesis of IRRs regarding the risk of CeVE (IRR=0.69, CI 0.57-0.84).

In the same IMID cohorts, the risk of MI was evaluated by pooling fully adjusted multivariate HRs and IRRs in separate analyses. In the TNFi-treated intervention groups, statistically significant 34% and 31% decreased risks were presented compared to the CSNB-receiving controls (HR=0.66, CI 0.50-0.87 and IRR=0.69, CI 0.60-0.81, respectively).

4.2. Study II. - Investigating the effect of TNF-inhibitors on the risk of heart failure in IMIDs

6,434 studies were identified during the systematic search. After the elimination of duplicate hits and further steps of title, abstract, and full-text selections, as well as citation chasing, 53 articles with the findings of 49 individual studies met the inclusion criteria.

45 studies were incorporated into the meta-analysis, synthesising data from more than 150,000 IMID patients.

The outcome of de novo HF was investigated in separate analyses incorporating both randomised and non-randomised data. The pooled effect size of the meta-analysis of RCT-derived data demonstrated no risk enhancement in the TNFi groups compared to the controls (RR=0.87, CI 0.60-1.25). Even based on the pooled effects of the subgroups with different IMID populations (RA, PsO/PsA and IBD) and TNFi agents (adalimumab, infliximab), TNFis did not increase the risk of de novo HF.

Data from four non-randomised observational studies involving RA patients could be included in the analysis of the assessment of the risk of worsening of HF. The pooled overall effect did not show a statistically significant risk increase in TNFi-receiving patients compared to non-TNFi-treated controls (RR=1.18, CI 0.69-2.00).

5. Conclusions

Based on our findings, TNFis significantly lower the risk of CV events in comparison with CSNBs. Earlier use of TNFis in the therapeutic sequence may contribute to the decrease in risk of atherosclerosis-driven CV events, thus improving the quality of life and life expectancy of IMID patients.

The present results suggest that TNFis do not enhance the risk of de novo HF, and they have no significant risk-increasing effect on worsening of HF. IMID therapeutic guidelines should be updated reflecting current findings on new-onset HF, whereas further investigations regarding the worsening of HF in TNFi-treated IMID populations are warranted.

6. Bibliography

Publications related to the thesis:

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