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Figure 1. Kaplan Meyer Survival Analyses. A. risk of immunogenicity according to the number of biosimilars infliximab received; B, risk of treatment interruption according to the presence of anti-drug antibodies (ADA); and C, treatment retention within the observation period


**OP0229** PHASE II CLINICAL TRIALS SYSTEMATICALLY OVERESTIMATE TREATMENT EFFECTS OF SUBSEQUENT PHASE III TRIALS IN RHEUMATOID ARTHRITIS

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Background: Phase 3 (P3) clinical trials are the mainstay of drug development in all areas of medicine, including rheumatology, allowing to determine safety and efficacy of new drugs on their way to approval. Historically, efficacy results of P3 trials have often been disappointing with respect to the expectations set by phase 2 (P2) trials. It is unclear whether these observations are reflection of a true bias or merely a play of chance.

Objectives: To systematically compare efficacy results of P2 versus P3 trials in RA and investigate potential determinants of efficacy differences.

Methods: We performed a systematic review of disease modifying anti-rheumatic drugs (DMARDs) tested in P2 trials in rheumatoid arthritis (RA) over the last 20 years for which also P3 trials exist. We searched Medline, EMBASE, and the
COCHLEAR TUBE VACCINATION FOR INFLUENZA IN PATIENTS WITH RHEUMATOID ARTHRITIS

**Objectives:** To estimate the effectiveness of influenza vaccine for patients with rheumatoid arthritis (RA). RA is associated with higher risk for influenza, and the vaccine is recommended in patients with inflammatory bowel disease (IBD), but data for RA patients with chronic inflammatory disease is limited. We used a systematic approach to evaluate the effectiveness of vaccination in this population.

**Methods:** We conducted a systematic review and meta-analysis of randomized controlled trials comparing vaccinated and unvaccinated patients with RA. The primary outcome was the rate of influenza infection, with secondary outcomes including adverse events and vaccine effectiveness measures.

**Results:** In total, 1290 abstracts were screened, of which 133 were included in the analysis. Summary estimates revealed that outcomes of P2 trials were systematically overestimated compared to P3 trials (ACR20: OR 1.40, 95% CI: 1.15-1.57; p=0.001), ACR50: OR 1.36; 95% CI: 1.21-1.54; p=0.001), and ACR70: (OR 1.39; 95% CI: 1.02-1.80; p=0.037). Exploration of determinants of this systematic bias revealed that inclusion criteria for minimum number of required swollen joints (IC-SJC) and tender joints (IC-TJC) as well as joint count used for inclusion (28 vs. 66/68 joint count) were significant determinants of efficacy differences. Figure 2 shows scatter plots of efficacy differences (shown as OR), revealing that higher IC-SJC and IC-TJC, as well as using the 66-JC instead of the 28-JC for study inclusion lead to a significantly lower chance of efficacy overestimation.

**Conclusion:** Our results reveal that Phase 2 clinical trials overestimate the treatment effects when compared with subsequent Phase 3 trials in RA. The identification of this systematic bias towards overestimation of efficacy by Phase 2 studies has implications for clinical practice, including the development and licensing of new compounds, as well as potential ethical implications.

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**OP230 EFFECTIVENESS OF INFLUENZA VACCINE IN TNF INHIBITORS TREATED PATIENTS**

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**Background:** Tumor Necrosis Factor-α inhibitors (TNFi) are immunosuppressive therapies that are known to increase infectious risk. Indeed, patients affected by TNFi may be at higher risk for influenza compared with healthy controls. Furthermore, mildly reduced seroconversion rate after influenza vaccination had been reported in TNFi-treated patients. Nonetheless the immune response is considered large enough to recommend influenza vaccination in all patients affected by rheumatoid arthritis, regardless of treatment. However, there are data showing that patients are not being vaccinated as recommended. In addition, given that subjects with autoimmune diseases treated with TNFi are at higher risk for influenza, the exact number needed to vaccinate (NNV) for this condition is still unknown.

**Objectives:** We sought to determine the NNV for influenza in TNFi treated patients and the cost for preventing one case of influenza compared with general population.

**Methods:** The present analysis included data from cohorts of healthy subjects [1] and TNFi treated patients [2]. We calculated NNV for preventing one case of influenza in each cohort. NNV is the required number of patients receiving vaccination to prevent one case of a given infectious disease. NNV is the inverse of the absolute risk reduction (ARR), which is calculated as follows: Control Event Rate (CER) – Experimental Event Rate (EER). In addition, the NNV gives us the opportunity to calculate the cost for preventing one case of influenza, assuming a cost per vaccine from 20 to 40 $.

**Results:** In total, 1290 abstracts were screened of which 133 were regarded as potentially relevant, with 44 trials (19 agents, 48 regimens, 17476 patients) finally included in the analysis. Summary estimates revealed that outcomes of P2 trials were systematically overestimated the subsequent P3 results for ACR20 (OR: 1.40; 95% CI: 1.15-1.57; p=0.001), ACR50 (OR: 1.36; 95% CI: 1.21-1.54; p=0.001), and ACR70 (OR: 1.39; 95% CI: 1.02-1.80; p=0.037). Exploration of determinants of this systematic bias revealed that inclusion criteria for minimum number of required swollen (IC-SJC) and tender joints (IC-TJC) as well as the joint count used for inclusion (28 vs. 66/68 joint count) were significant determinants of P2/P3 efficacy differences. Figure 2 shows scatter plots of efficacy differences (shown as OR), revealing that higher IC-SJC and IC-TJC, as well as using the 66-JC instead of the 28-JC for study inclusion lead to a significantly lower chance of efficacy overestimation.

**Conclusion:** When estimating the effectiveness of vaccinations, clinicians should always include the calculation of the NNV and not only the calculation of relative risk, which might be misleading. The difference in NNV for influenza between healthy individuals and TNFi treated patients is due to a greater absolute risk for influenza in the latter group. The present analysis provides further evidence on the effectiveness of influenza vaccination in patients affected by rheumatoid arthritis receiving treatment with TNFi and should represent a call-to-action for all rheumatologists to consider vaccination in such patients.

**REFERENCES:**


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**Figure 1. Number Needed to Vaccinate (NTV) for influenza in the general population and in patients treated with Tumor Necrosis Factor-α inhibitors (TNFi)**