Title: An Economic Evaluation of Stopping versus Continuing TNF-Inhibitor Treatment in Rheumatoid Arthritis Patients in Remission or Low Disease Activity: results from the POET randomized trial.

Running Head: An Economic Evaluation of Stopping TNFi in RA patients in stable low disease activity

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Objective: To evaluate, from a societal perspective, the incremental cost-effectiveness of withdrawing tumor necrosis factor inhibitors (TNFis) compared to continuation of these drugs within a one-year randomized trial among patients with rheumatoid arthritis (RA) having longstanding stable disease activity or remission.

Methods: Data were collected from a pragmatic, open label trial. Cost-utility analysis was performed using the non-parametric bootstrapping method and a cost-effectiveness acceptability curve was constructed using the net-monetary benefit (NMB) framework, where a willingness-to-accept threshold (WTA) was defined as the minimal cost saved that a patient accepted for each quality-adjusted life year (QALY) lost.

Results: 531 patients were randomized to the Stop Group and 186 patients to the Continue Group. Withdrawal of TNFis resulted in more than 60% reduction of the total drug cost, but led to an increase of about 30% in the other healthcare expenditure. Compared to continuation, stopping TNFis resulted in a mean yearly cost saving of €7,133 (95% CI, [€6,071, €8,234]) and was associated with a mean loss of QALYs of 0.02 (95% CI, [0.002, 0.040]). Mean saved cost [95% CI] per QALY lost and per extra flare incurred in the Stop group compared to the Continuation group was €368,269 [€155,132, €1,675,909] and €17,670 [€13,650, €22,721], respectively. At a WTA of €98,438 per QALY lost, the probability that stopping TNFis is cost-effective was 100%.

Conclusion: Although an official WTA is not defined, the mean saved cost of €368,269 per QALY lost seems acceptable in The Netherlands, given existing data on the willingness-to-pay.
Keywords: Rheumatoid arthritis; Anti TNF; Health Economic Evaluations.

Rheumatoid arthritis (RA) is a progressive, immune-mediated inflammatory disease that has a prevalence of around 1% in developed countries (1). The disease is characterized by synovial inflammation and with time may involve articular damage, disability and extra-articular manifestations. Besides its negative impact on the health of individual patients, RA imposes a significant and increasing economic burden on health-care systems and societies in the form of healthcare resource utilization and (paid) productivity loss (2).

The main goal in the treatment of RA is to suppress inflammatory activity to control pain and prevent unfavorable outcomes such as structural damage and functional disability. Accumulating evidence suggests that optimal clinical outcomes may be achieved if treatment is started early and adjusted to reach predefined disease activity targets (3, 4). The subpopulation of patients receiving biological disease modifying anti-rheumatic drugs (bDMARDs) including tumor necrosis factor inhibitors (TNFis) in this treat-to-target strategy has increased over time and accounted for up to 20% of the population of RA patients in various Western healthcare systems (5, 6). Although it is widely believed that the introduction of bDMARDs has contributed to the overall improved clinical picture of severe RA, particularly in the methotrexate refractory population (7), their high cost has raised the question of whether bDMARDs could be discontinued in patients who achieved long-term stable controlled disease, without negatively affecting their health (8). As healthcare budgets are limited and money can be spent only once, savings from stopping treatment with bDMARDs could be used to reinvest in other treatments or increase access to bDMARDs to a larger proportion of the population of patients with RA.

The recently completed Potential Optimalisation of Expediency and Effectiveness of TNFis (POET) trial aimed to evaluate the clinical course of patients withdrawn from their TNFis,
compared with that of patients who remained on TNFis (9). The results showed that, patients who were withdrawn from their TNFis were more than three times as likely to experience a disease flare compared with patients who continued their TNFis. However, disease control could typically be quickly regained upon TNFi restart. Although the withdrawal of TNFis is evidently associated with lower medication costs, this may be offset by higher non-drug related healthcare costs or by lasting impact on patients’ overall quality of life. From the health economic point of view, it is currently unclear whether the benefits of discontinuation of TNFis outweighs the harms. The present study aimed to evaluate, from a societal perspective, the one-year trial based cost-utility and cost-effectiveness of withdrawing TNFis compared to continuation of these drugs in RA patients with longstanding stable disease to inform rheumatologists and patients about balance between savings and health forgone.

Patients and Methods

Study design and patients

The study outcomes and design of the POET study (NTR3112) are described in detail elsewhere (9). Briefly, this pragmatic, open label trial was performed at 47 rheumatology centers in The Netherlands and included 817 adult patients fulfilling the American College of Rheumatology 1987 classification criteria for RA who were treated with TNFis for at least one year. In addition, patients met one of the following criteria: (1) DAS28 < 3.2 for at least 6 months preceding inclusion (n = 627), or (2) perceived by the rheumatologists as having remission or low disease activity for at least 6 months prior to inclusion, with DAS28 <3.2 at baseline and C-reactive protein level < 10 mg/L at least once in the six-month period prior to the inclusion (n = 145). Patients were randomized to either Stop group (n = 551) or Continuation group (n = 286). After inclusion, TNFis were withdrawn in the Stop group but maintained in the Continuation group. Any other treatment decisions were made by rheumatologists with their patient and continued
unchanged as much as possible in both groups. The primary outcome of the study was occurrence of disease flares, defined as DAS28 increase ≥ 0.6 compared to the baseline and the current DAS28 level ≥ 3.2.

Follow-up procedures

Patients were assessed at baseline and at least once every 3 months thereafter, for a period of 1 year. At each visit, components of DAS28, Health Assessment Questionnaire Disability Index (HAQ-DI) (10, 11) and EuroQol 5-dimensional 3-level (EQ-5D-3L) questionnaire (12) were evaluated, laboratory tests conducted, and patient-reported outcomes collected. Patient reported outcomes included adverse events, days of sick leave and frequencies of healthcare resource utilization. Restart of a TNFi was allowed when a flare occurred; for ethical reasons this included cases where patient’s perception of a flare could not be objectively verified.

Health economic outcomes

At each visit, patients answered the EQ-5D-3L questionnaire and reported the frequencies of healthcare resource utilization and number of days of sick leave (in those with a paid job) during the past 3 months. The healthcare resource utilization included visits to rheumatologists and general practitioners, visits to nurse specialists, physiotherapists and psychologists, numbers of diagnostic and laboratory tests, days in hospital and hours of formal and informal care.

For each patient, their health utility at 3-month visits was computed using the Dutch tariffs for EQ-5D-3L (13), and quality-adjusted life years (QALYs) computed as the area under the EQ-5D-3L curve. Non-drug direct costs were calculated based on patient reported frequencies of healthcare resource utilization. The unit costs were retrieved from the Dutch Guideline for
Economic Evaluations in Healthcare. Drug costs were calculated based on the doses of drug used and the medication prices. Indirect costs of those patients with a paid job were calculated using the friction-cost method with a 3 month-friction period and based on the number of hours absent from work and the average wage per hour for each age group and gender (14). The unit costs and prices published before the current year (2016) were adjusted to the current year using the consumer price index for the Netherlands (15). Costs were not discounted because of the short time horizon of 12 months.

**Statistical and cost-effectiveness analyses**

Between 10% and 15% of observations contained missing values for costs or utilities (see Supplementary document for details). For the cost-effectiveness analysis, these were replaced with estimates using multiple imputation (MI) as recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) for cost-effectiveness analysis alongside clinical trials (16). For each of the 10 imputed data sets, cost-effectiveness analysis (CEA) was performed using the non-parametric bootstrapping method (17). Five thousand bootstrap samples were generated, from which the expected values of costs and QALYs over the one-year follow-up in each treatment group and of the ratios of incremental cost to incremental QALYs or flares (ICERs) were computed (18). Manca et al recommended an adjustment of QALYs before calculation of ICERs when there was an imbalance in the mean baseline health utility between two trial arms (19). Because mean baseline health utility and other patient characteristics in our study were almost equal between the Stop and Continuation groups, in the main analyses and presentation of the results we used QALYs and costs unadjusted for these negligible differences. To examine the effect of QALYs and costs adjustment on ICERs, we used the regression-based method proposed by Manca et al (19), in which linear regression models for patient-specific QALYs and costs were fitted to the observed data with predictors for QALYs.
being treatment and baseline health utility, and predictors for costs being treatment, age, sex, disease duration, DAS28 and HAQ-DI. Then, we used the coefficients for the treatment as the differential QALYs and costs for the adjustment. We applied a Box-Cox transformation for QALYs and a log-transformation for costs to meet the assumptions of normal distribution and equal variance of the error term in the linear models (20). The results were pooled across imputed datasets using Rubin’s rules (21) to take into account the uncertainty introduced by the missing data. Because the distribution of costs was skewed, the “approximate bootstrap confidence” (ABC) algorithm (22) was used to estimate the confidence intervals (CIs), instead of the usual symmetric confidence interval proposed by Rubin (21). For each imputed data set, a confidence density curve was constructed for each of the outcome variables. The 10 confidence density curves were then combined by averaging the y-values to obtain the average density function, based on which the 95% CI was established by determining the areas under the curve that correspond to 5% and 95% percentiles. For each imputed data set, a cost-effectiveness acceptability curve (CEAC) was constructed using the net-monetary benefit (NMB) framework (23), where an expected NMB was calculated as the difference between the willingness-to-accept threshold (WTA) for each QALY lost times the mean QALYs (\( \bar{E}_i \)), and the mean cost obtained from each bootstrap replication (\( \bar{C}_i \)): \( \text{NMB} = WTA \times \bar{E}_i - \bar{C}_i \). The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) were followed to report the present study (see the checklist in the supplemental document).

Results

Baseline characteristics were similar in both groups (Table 1). The majority of the patients had longstanding, erosive disease and utility scores reasonably close to general population norms (24). The sample was further characterized by low disease activity at baseline according to DAS28, as per the inclusion criteria and low disability according to HAQ-DI.
Health outcomes

Mean DAS28 and HAQ-DI scores in the Continuation Group were almost stable over time (Figure 1), while in the Stop group mean DAS28 score increased from baseline to month 3 and then gradually decreased during the rest of the year, and mean HAQ-DI score slightly increased over time. Post-hoc analyses revealed significant differences in DAS28 scores at all follow up visits (p-values < 0.01), except baseline (p-value = 0.27). No significant difference in HAQ-DI scores between the two groups at any time point was observed.

The percentages of patients with 1 or 2 flares within 12 months was 41.1% and 8.1% in the Stop Group and 15.4% and 1.4% in the Continuation group. No patients and only 0.6% of patients had 3 flares in the Continuation and Stop groups, respectively. On average, within 12 months each patient experienced 0.59 flares (95% CI, [0.53, 0.64]) in the Stop group, and 0.18 (95% CI, [0.13, 0.24]) flares in the Continuation group.

Mean health utility in the Continuation group slightly deteriorated during the first 6 months and then remained relatively stable during the rest of the year, while that in the Stop group decreased within the first 3 months and then slightly increased until end of the year (Figure 2). Except for month 3 (p-value = 0.0005), mean health utility was not significantly different at any time points between the two groups (p-values > 0.05).

Healthcare, medication and sick leave costs and QALYs

Table 2 shows means and 95% CIs of non-drug healthcare costs, drug costs and sick leave costs (in Euro) and of QALYs per patient per year in the two treatment strategies. A detailed overview of healthcare resource utilization in each category at baseline and cumulative over 1 year as well
as the corresponding unit prices is provided in the supplementary document (Tables S1-S5). Withdrawal of TNFIs resulted in more than 60% reduction of the total drug cost, but led to an increase of about 30% of the other healthcare expenditure. Sick leave cost in the Stop group was slightly lower than that in the Continuation group, although the difference between the two groups was insignificant. Since the cost of TNFIs was much larger than the increased expenditure in other cost components, the mean total cost incurred by each patient per year in the Continuation group (€14,740; 95% CI, [€13,913, €15,676]) was almost double that in the Stop group (€7,607; 95% CI, [€7000, €8,261]). Mean QALYs [95% CIs] per patient in the Stop and Continuation groups were 0.79 [0.781, 0.805] and 0.81 [0.799, 0.829], respectively.

Incremental cost-effectiveness and uncertainty

An average patient in the Stop group may save €7,133 (95% CI, [€6,071, €8,234]) for society, but would lose 0.022 QALY (95% CI, [0.002, 0.040]) per year and experience 0.41 (95% CI, [0.33, 0.48]) more flares compared to an average patient in the Continuation group. Mean saved cost [95% CI] per QALY lost and per extra flare incurred in the Stop group compared to the Continuation group was €368,269 [€155,132, €1,675,909] and €17,670 [€13,650, €22,721], respectively. When QALYs and costs were adjusted for differences in baseline health utility and patient characteristics, mean saved cost [95% CI] per QALY lost in the Stop group compared to the Continuation group (€371,457 [€156,291, €1,736,887]) was slightly higher than that when no adjustment was made. Because the difference in mean sick leave costs between the two groups was very small, mean costs saved [95% CI], from the healthcare perspective, per QALY lost (€366,642 [€152,396, €1,662,057]) and per flare increase (€17,587 [€13,575, €22,642]) were similar to those from the
societal perspective. Hereafter, we focused on the outcomes and interpretation from the societal perspective.

The scatter plot of the incremental mean costs and QALYs resulting from 50,000 bootstrapped replications for 10 imputed data sets is provided in Figure 3. All differences in mean costs were negative. About 1.5% of all data points fell in the south-east quadrant (i.e. saved cost with increased QALYs), indicating that the probability that withdrawal of TNF-inhibitors is cost-effective at any level of WTA is negligible. At WTAs of €330,450 and €98,438, the probabilities that withdrawal of TNF-inhibitors were cost-effective were 0.5 and 1.0, respectively (Figure 4). If stopping TNFis is considered as the baseline comparator, it was almost certain that the continuation of TNFis was not cost-effective at a willingness-to-pay (WTP) of €100,000 per QALY gained.

Discussion

Our analysis shows that stopping TNFis in RA patients with stable controlled disease (remission or low disease activity) can save considerable cost but results in a small QALY loss. At the beginning of this century, TNFis were developed, studied and introduced to control inflammatory disease activity in patients with RA. Despite increasing budget impact over the first fifteen years since the introduction of these drugs, evidence on the possibility to discontinue TNF in the maintenance phase is still sparse. Therefore, patients are frequently kept on TNF indefinitely. Up to now, TNFis have been recommended in most of the developed countries for management of RA and reimbursed for patients with persistently high disease activity despite adequate treatment with at least 2 csDMARDs (25-28). These recommendations were predominantly based on evidence on the favorable cost-effectiveness ratio of TNF therapy compared to csDMARDs in patients with severe disease. For instance, a recent systematic
literature review on economic aspects of treatment with TNFis to inform clinical recommendations by the European League Against Rheumatism (EULAR) showed that the incremental cost of the use of a TNFi after failure of 2 csDMARDs per QALY gain was less than €60,000 (conversion applied) in 14 out of 18 studies (29). Regardless of the majority of studies with outcomes in favor of the use of TNFis in this population, concerns continue to be raised about the substantial impact of therapy with TNFis on the healthcare budgets owing to the high prices of these drugs. For economic reasons, withdrawal of TNFis has therefore been considered in patients with sustained low disease activity.

So far, about a dozen studies examining the effects of discontinuing TNFis on clinical outcomes have been published (30-35). Due to the heterogeneity in study designs, characteristics of patients, definitions of low disease activity and permission of restarting TNFis when failure was observed, the results between studies differed remarkably; the proportions of patients who were free from failure after discontinuation of TNFis ranged from 0% to 33% at 7 months, and from 13% to 80% at 12 months (31). Despite the fact that high treatment costs are a frequently cited motivation to conduct such studies, unfortunately no previous discontinuation studies reported on preference-based health valuation such as EQ-5D, or healthcare costs which are important to inform health policy decisions. In the present study, we showed that, except for the first follow-up point after baseline, the mean health utility did not significantly differ over time between patients in the Stop and Continuation groups. These results suggest that discontinuing TNFis in patients with long-term stable disease is a strategy that over the course of 1 year is associated with considerable saved cost and negligible loss of quality of life. Very similar conclusions were reached in the DRESS down titration study in which it was found that when using a TNFi down titration approach guided by disease activity, an amount of €390,493 could be saved for each QALY lost compared with continued tight control treatment. Together, these findings suggest...
significant potential for disinvestment decisions (i.e. to stop subsidizing therapies that are not cost-effective) (36). This could potentially free up resources that could be reallocated to other more cost-effective interventions. One way to do this would be to look for scope for implementing other more cost-effective interventions on the patients formerly receiving TNFis, as any improvement in their health status could offset the loss in QALYs due to discontinuation. Such an approach would avoid having to make trade-offs involving reducing the health of patients with RA.

While there is no explicit WTA threshold that could be used to judge whether or not TNFis should be discontinued it is useful to consider the threshold for WTP which is suggested to be between €20,000 and €73,000 per QALY in the Netherlands (37). The estimated saving per QALY lost of €368,269 is much higher than the maximal bound of this threshold range, suggesting that it would be cost-effective to discontinue TNFis in the maintenance phase while the patients are in a state of low disease activity or remission. Adjustment of QALYs and costs for differences in baseline health utility and patient characteristics resulted in a slightly higher saving than the above-mentioned value, which increases the likelihood that stopping TNFis is cost-effective.

Our study has strengths and weaknesses. It is based on the largest RCT on discontinuing TNFis in RA patients in stable low disease activity, with high-quality data owing to a strictly electronic data collection protocol. Generalizability of the results to the overall population of patients withdrawing from TNFis is probably high, since it was a pragmatic trial with relatively few inclusion and exclusion criteria were maintained in POET study. We used advanced methods, i.e. combination of multiple imputation, bootstrap and ABC algorithm, to capture the uncertainty surrounding the study results. However, our findings on the cost-effectiveness of stopping
TNFis are valid only for an intervention duration of 12 months. Studies on the WTA thresholds in patients with RA are important to support decision making. Since patients with different disease durations and numbers of failed TNFis may respond differently to the discontinuation of the current TNFi, more research of response to discontinuation is needed.

In conclusion, stopping TNFis in RA patients with stable low disease activity, on average, was associated with a cost saving of €7,133, a loss of 0.022 QALY and an increase of 0.41 flares per patient per year. Although an official WTA threshold is not available, the mean saved cost of €368,269 per QALY lost we found would be cost-effective in The Netherlands, given existing data on the WTP and the WTA/WTP ratio. If the WTA threshold is €100,000, the probability that stopping TNFis is cost-effective is approximately 1.

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Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stop group (n = 531)</th>
<th>Continuation group (n = 286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>60.1 (11.8)</td>
<td>59.7 (10.6)</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>362 (68)</td>
<td>188 (66)</td>
</tr>
<tr>
<td>Mean disease duration in years (SD)</td>
<td>12.0 (8.8)</td>
<td>11.1 (8.4)</td>
</tr>
<tr>
<td>RF positive, no. (%)</td>
<td>238 (67.5)</td>
<td>178 (67.4)</td>
</tr>
<tr>
<td>Anti-CCP positive, no. (%)</td>
<td>332 (68.3)</td>
<td>179 (67.8)</td>
</tr>
<tr>
<td>Erosive disease, no. (%)</td>
<td>305 (62.8)</td>
<td>152 (57.6)</td>
</tr>
<tr>
<td>Mean DAS28 (SD)</td>
<td>1.98 (0.76)</td>
<td>2.05 (0.73)</td>
</tr>
<tr>
<td>Mean HAQ (SD)</td>
<td>0.63 (0.59)</td>
<td>0.62 (0.55)</td>
</tr>
<tr>
<td>Mean EQ-5D-3L score (SD)</td>
<td>0.83 (0.16)</td>
<td>0.84 (0.13)</td>
</tr>
<tr>
<td>Patient on a TNF-inhibitor, no (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>271 (51.1)</td>
<td>129 (45.1)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>213 (40.2)</td>
<td>133 (46.5)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>25 (4.7)</td>
<td>14 (4.9)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>15 (2.8)</td>
<td>8 (2.8)</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>7 (1.2)</td>
<td>2 (0.7)</td>
</tr>
</tbody>
</table>

RF = rheumatoid factor; Anti-CCP = anti-cyclic citrullinated peptide antibodies; DAS28 = disease activity score in 28 joints; HAQ= Health Assessment Questionnaire; EQ-5D-3L = five-dimensional 3-level EuroQol; TNF = tumor necrosis factor-alpha.
Table 2. Mean costs (in Euro) and QALY [95% CIs] per patient per year in the two treatment strategies

<table>
<thead>
<tr>
<th></th>
<th>Stop group</th>
<th>Continuation group</th>
<th>Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-drug health care</td>
<td>2,122</td>
<td>1,663</td>
<td>459</td>
</tr>
<tr>
<td>cost</td>
<td>[1,684, 2,563]</td>
<td>[1,384, 1,958]</td>
<td>[70, 890]</td>
</tr>
<tr>
<td>Drug cost</td>
<td>4,894</td>
<td>12,450</td>
<td>-7,556</td>
</tr>
<tr>
<td></td>
<td>[4,396, 5,402]</td>
<td>[11,427, 13,472]</td>
<td>[-8,547, -6,629]</td>
</tr>
<tr>
<td>csDMARD</td>
<td>325</td>
<td>324</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>[220, 461]</td>
<td>[230, 471]</td>
<td>[-98, 121]</td>
</tr>
<tr>
<td>TNFi</td>
<td>4,568</td>
<td>12,126</td>
<td>-7,558</td>
</tr>
<tr>
<td></td>
<td>[4,070, 5,067]</td>
<td>[11,106, 13,145]</td>
<td>[-8,534, -6,643]</td>
</tr>
<tr>
<td>Sick leave cost</td>
<td>591</td>
<td>626</td>
<td>-35</td>
</tr>
<tr>
<td></td>
<td>[450, 735]</td>
<td>[452, 804]</td>
<td>[-226, 155]</td>
</tr>
<tr>
<td>Total cost</td>
<td>7,607</td>
<td>14,740</td>
<td>-7,133</td>
</tr>
<tr>
<td></td>
<td>[7,001, 8,261]</td>
<td>[13,913, 15,676]</td>
<td>[-8,234, -6,071]</td>
</tr>
<tr>
<td>QALYs</td>
<td>0.79</td>
<td>0.81</td>
<td>-0.022</td>
</tr>
<tr>
<td></td>
<td>[0.781, 0.805]</td>
<td>[0.799, 0.829]</td>
<td>[-0.040, -0.002]</td>
</tr>
<tr>
<td>ICER (€ per QALY)</td>
<td></td>
<td></td>
<td>368,269</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[155,132, 1,675,909]</td>
</tr>
</tbody>
</table>

csDMARD, conventional synthetic disease-modifying antirheumatic drug; TNFi, tumor necrosis factor inhibitor; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio
Figure legends:

Figure 1. Mean DAS28 and HAQ-DI at different points in time during the 1-year follow-up in the two treatment strategies. The vertical bars represent 95% confidence intervals.

Figure 2. Mean EQ-5D-3L scores at different points in time during the 1-year follow-up in the two treatment strategies. The vertical bars represent 95% confidence intervals.

Figure 3. Scatter plot of incremental mean cost against incremental mean QALYs of Stop strategy compared to Continuation strategy. Each data point was obtained from one bootstrap replication.

Figure 4. Cost-effectiveness acceptability curve for Continuation and Stop strategies.