# Benefit-risk Analysis of Adalimumab and Alternative Treatments for Moderate to Severe Rheumatoid Arthritis

PMS5

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## Background

- Rheumatoid arthritis (RA) is a chronic disease characterized by inflammation of the lining or synovium of the joints and can lead to long-term joint damage resulting in chronic pain, loss of function, and disability[1]
- Patients with RA may be treated with disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), or a combination of MTX and anti–tumor necrosis factor (TNF) agents, such as adalimumab (ADA) or infliximab (IFX)[2–4]
- Understanding to what extent the benefits of various pharmacotherapies outweigh the risks is important for clinicians prescribing therapies for RA
- Benefit-risk analyses comparing different treatments for RA are limited

## Objectives

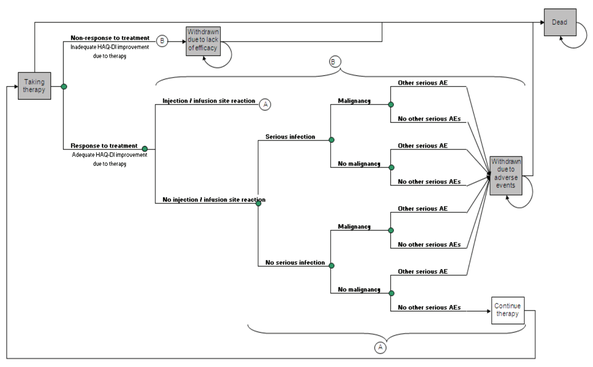
- To compare treatment-related risks vs. improvements in outcomes in terms of net health benefit (NHB) for 3 treatments for moderate to severe RA:
  - MTX alone,
  - ADA in combination with MTX, and
  - IFX in combination with MTX

## Methods

### Benefit-Risk Model

- An individual-level simulation model was developed in which a cohort of patients with RA initiating treatment progressed at 6-month intervals for 10 years or until withdrawal from therapy
- As patients progressed on therapy, they accrued both benefits and risks **(Figure 1)**

### Figure 1. Schematic Representation of Benefit-Risk Model




AE = adverse event; HAD-DI = Health Assessment Questionnaire Disability Index.
"A" designates the portion of the model following infusion site reaction outcomes, while "B" designates the portion that follows treatment response outcomes.

### RA Therapies

- Patients observed under each of 3 treatment regimens for RA **(Table 1)**

### Table 1. Treatments for RA

| | ADA | MTX | IFX |
|---|---|---|---|
| MTX alone | — | 7.5 mg weekly | — |
| ADA + MTX | 40 mg every 2 weeks | 7.5 mg weekly | — |
| IFX + MTX | — | 7.5 mg weekly | 210 mg at weeks 0, 2, and 6, then every 8 weeks |

ADA, adalimumab; IFX, infliximab; MTX, methotrexate; RA, rheumatoid arthritis.

### Patient Populations

- **MTX-naïve:** patients with high level of RA disease activity who did not receive previous treatment with DMARDs
- **DMARD-failure:** patients with moderate or high RA disease severity who did not respond to DMARDs

### Benefits

- Immediate response at the start of therapy
  - Measured by American College of Rheumatology (ACR) criteria for improvement from baseline in disease activity (ACR20, ACR50, and ACR70, representing improvement of 20%, 50%, and 70%, respectively)
- Reduced progression of disease
  - Measured by Health Assessment Questionnaire Disability Index (HAQ-DI) scores

### Risks

- Withdrawal due to lack of efficacy (LOE)
- Adverse events (AEs) commonly associated with treatment and that led to withdrawal, including serious infections, malignancy, and other negative outcomes
- Injection and infusion site reactions, which were counted as AEs but did not affect withdrawal

### Outcomes

- Average years on therapy per patient
- Percentage of patients withdrawn from therapy (total, due to LOE, due to AEs, and due to death)
- Quality-adjusted life-years (QALYs) accrued due to benefits
- QALYs accrued due to risks (total)
- NHB was measured in discounted QALYs
- Benefits and risks were associated with increments and decrements in QALYs, respectively

### One-way Sensitivity Analyses

- The robustness of model assumptions and parameters was tested by examining the effect of change parameters in 1-way sensitivity analyses
- Effects of differing individual parameters were examined using plausible ranges of values from the literature,[5–17] 95% confidence intervals (CIs), and by varying estimates by ± 20%

## Results

### Study Populations

- The baseline model was run for 15 000 individuals from the MTX-naïve and DMARD-failure populations
- Because patients in the DMARD-failure population had already received treatment for RA, they had RA for a longer period of time than patients in the MTX-naïve population **(Table 2)**

### Table 2. Characteristics of Study Populations

| | MTX-Naïve | DMARD-Failure |
|---|---|---|
| Women, % | 71 | 77 |
| Average age (years) | 50.4 | 55.5 |
| Duration of RA (years) | ≤3 | 11–13 |
| HAQ-DI at start of treatment, mean (SD) | 1.56 (0.686) | 1.64 (0.144) |

DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire Disability Index; MTX, methotrexate; RA, rheumatoid arthritis.
Assumptions regarding the sex, age, and HAQ scores of MTX-naïve[13,14] and DMARD-failure[15–17] patients were made on the basis of previously studied populations.

### MTX-Naïve Population

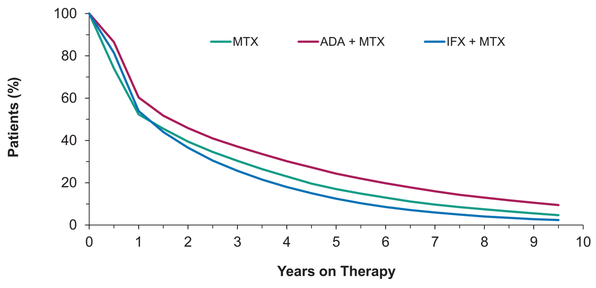
- Overall, patients treated with ADA + MTX remained on therapy longer than patients treated with IFX + MTX or MTX alone **(Table 3 and Figure 2)**
- Patients treated with ADA + MTX had more benefits in QALYs compared with patients in the other groups and more risk decrements in QALYs compared with patients on MTX **(Table 3)**
- ADA + MTX had higher net health benefits than MTX alone and IFX + MTX **(Table 3)**
- Compared with patients treated with ADA + MTX or IFX + MTX, those treated with MTX alone were more likely to withdraw due to LOE, were less likely to withdraw due to AEs, and accrued fewer QALY decrements due to risks **(Table 3 and Figure 3)**
- Patients treated with IFX + MTX had a higher incidence of withdrawals due to AEs, which contributed to a shorter time on therapy compared with patients in the other 2 groups **(Table 3 and Figure 3)**
- Withdrawal due to death was qualitatively higher for ADA + MTX compared with the other 2 groups **(Figure 3)**. This is due to the greater length of time spent on ADA + MTX therapy vs. another therapy. As time on therapy increases, so does a patient's age, and consequently, the likelihood of death from any cause

### Table 3. Predicted Outcomes Over 10 Years: MTX-Naïve Population

| Outcome | ADA + MTX | MTX | IFX + MTX |
|---|---|---|---|
| Years on therapy PP (95% CI) | 3.31 (3.26, 3.36) | 2.71[a] (2.66, 2.75) | 2.46[a] (2.42, 2.49) |
| Withdrawn from therapy, % | | | |
| Due to LOE | 41.5 | 62.3 | 36.8 |
| Due to AEs | 50.3 | 35.0 | 65.0 |
| Benefits in QALYs PP (95% CI) | 1.4132 (1.3938,1.4326) | 1.0917[a] (1.0762, 1.1072) | 1.0870[a] (1.072, 1.102) |
| Benefits in QALYs PP per year on therapy | 0.4625 | 0.4032 | 0.4423 |
| Risk decrements in QALYs PP (95% CI) | 0.0166 (0.0162, 0.0171) | 0.0122[a] (0.0118, 0.0126) | 0.0363[a] (0.0357, 0.0369) |
| NHB in QALYs PP (95% CI) | 1.3965 (1.3771, 1.4160) | 1.0795[a] (1.0640, 1.0950) | 1.0507a (1.0356, 1.0658) |
| Incremental NHB in QALYs PP vs. ADA | | -0.3170[a] | -0.3458[a] |

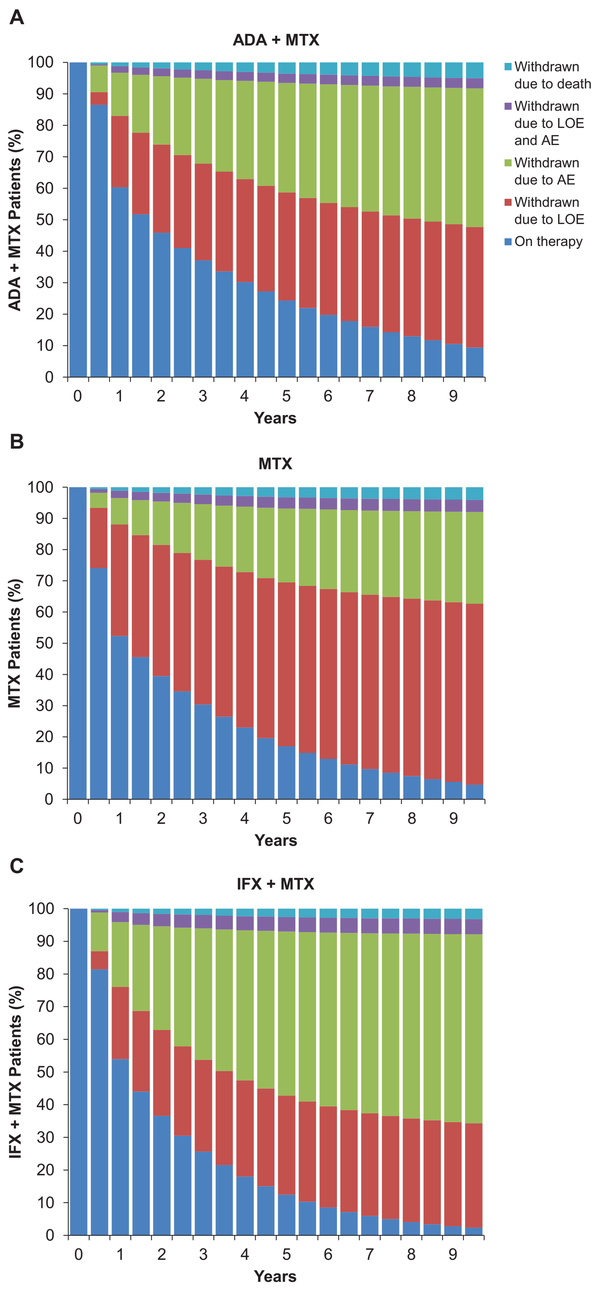
ADA, adalimumab; AE, adverse event; CI confidence interval; IFX, infliximab; LOE, lack of efficacy; MTX, methotrexate; NHB, net health benefit; PP, average per patient; QALY, quality-adjusted life-year.
[a]Statistically significant difference from ADA at the *P* = .05 level.

### Figure 2. Percentage of Patients MTX-Naïve Population Still on Therapy Over Time




ADA, adalimumab; IFX, infliximab; MTX, methotrexate.

### Figure 3. Distribution of Patients in the MTX-Naïve Population by Status Over Time




ADA, adalimumab; AE, adverse event; LOE, lack of efficacy; MTX, methotrexate.

### DMARD-Failure Population

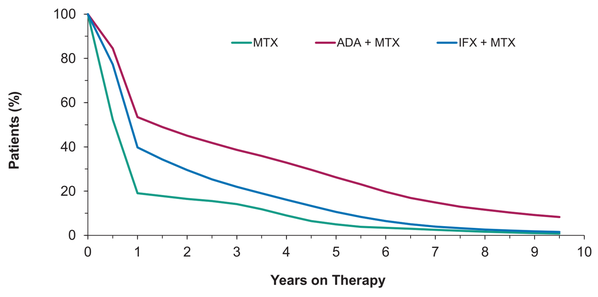
- Overall, patients treated with ADA + MTX remained on therapy longer than patients treated with IFX + MTX or MTX alone **(Table 4 and Figure 4)**
- Patients treated with ADA + MTX were less likely to withdraw from therapy due to LOE and had more benefits in QALYs compared with patients in the other groups. They also had more risk decrements in QALYs compared with patients on MTX **(Table 4)**
- ADA + MTX had higher net health benefits than MTX alone and IFX + MTX **(Table 4)**
- Compared with patients treated with ADA + MTX or IFX + MTX, those treated with MTX alone were more likely to withdraw due to LOE, were less likely to withdraw due to AEs, and accrued fewer QALY decrements due to risks **(Table 4 and Figure 5)**
- Patients treated with IFX + MTX had a higher incidence of withdrawals due to AEs compared with the other 2 groups **(Table 4 and Figure 5)**
- As was observed for the MTX-naïve population, withdrawal due to death was qualitatively higher for ADA + MTX compared with the other 2 groups **(Figure 5)**

### Table 4. Predicted Outcomes Over 10 Years: DMARD-Failure Population

| Outcome | ADA + MTX | MTX | IFX + MTX |
|---|---|---|---|
| Years on therapy PP (95% CI) | 3.33 (3.28, 3.38) | 1.44[a] (1.41, 1.46) | 2.11[a] (2.08, 2.15) |
| Withdrawn from therapy, % | | | |
| Due to LOE | 41.9 | 85.1 | 47.2 |
| Due to AEs | 49.3 | 18.4 | 56 |
| Benefits in QALYs PP (95% CI) | 1.3932 (1.3729,1.4135) | 0.5735[a] (0.5619, 0.5850) | 0.8946[a] (0.8800, 0.9092) |
| Benefits in QALYs PP per year on therapy | 0.4181 | 0.3989 | 0.423 |
| Risk decrements in QALYs PP (95% CI) | 0.0159 (0.0155, 0.0164) | 0.0065[a] (0.0062, 0.0068) | 0.0301[a] (0.0296, 0.0307) |
| NHB in QALYs PP (95% CI) | 1.3773 (1.3570, 1.3976) | 0.5670[a] (0.5554, 0.5785) | 0.8645[a] (0.8499, 0.8790) |
| Incremental NHB in QALYs PP vs. ADA | | -0.8103[a] | -0.5128[a] |

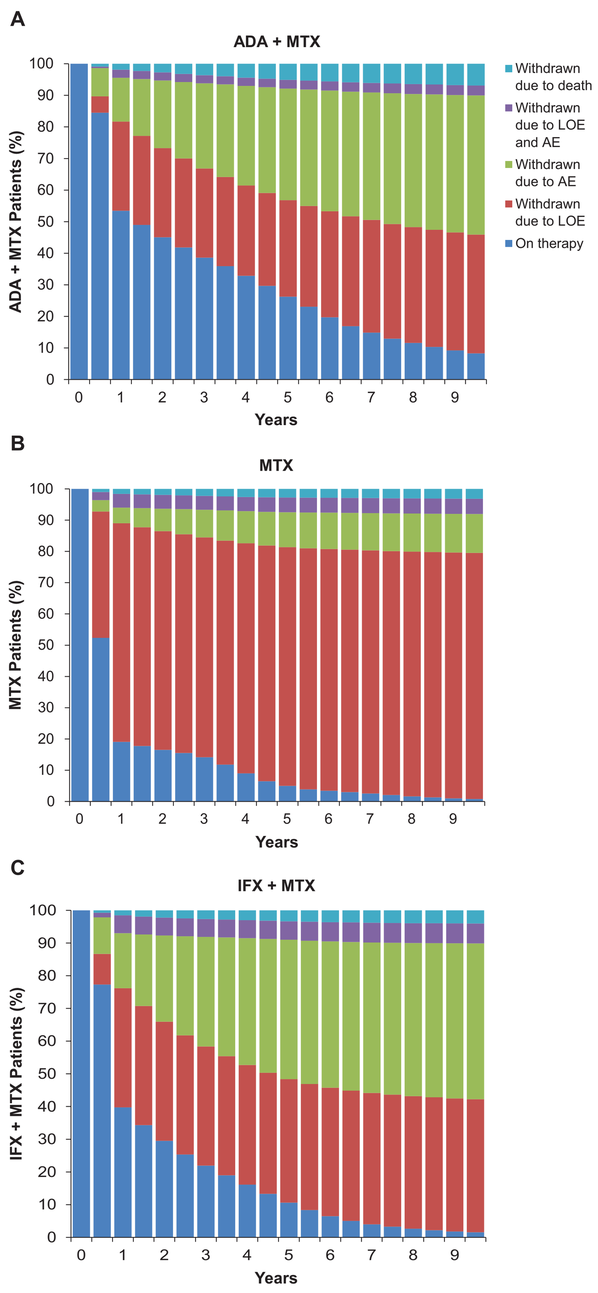
ADA, adalimumab; AE, adverse event; CI confidence interval; IFX, infliximab; LOE, lack of efficacy; MTX, methotrexate; NHB, net health benefit; PP, average per patient; QALY, quality-adjusted life-year.
[a]Statistically significant difference from ADA at the P = .05 level.

### Figure 4: Percentage of Patients in the DMARD-Failure Population Still on Therapy Over Time




ADA, adalimumab; DMARD, disease-modifying antirheumatic drug; IFX, infliximab; MTX, methotrexate.

### Figure 5. Distribution of Patients by Status Over Time in the DMARD-Failure Population

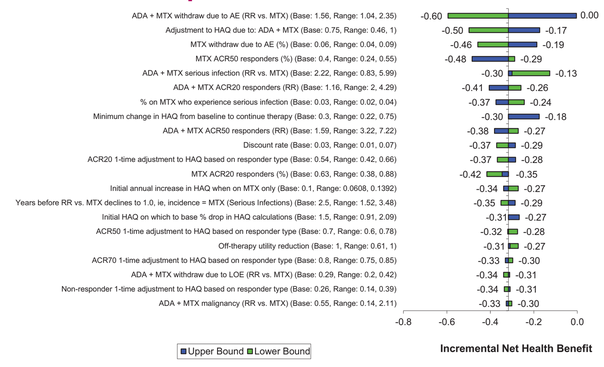



ADA, adalimumab; AE, adverse event; DMARD, disease-modifying antirheumatic drug; LOE, lack of efficacy; MTX, methotrexate.

### Sensitivity Analyses

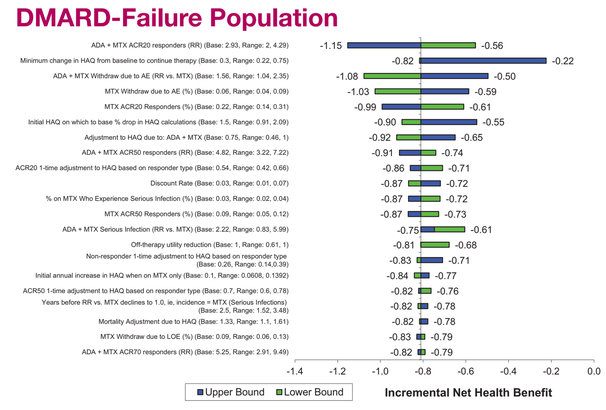
- In both populations, the incremental NHB was most sensitive to changes in the risks of AEs, impact of therapies on HAQ progression, and ACR response rates **(Figures 6 and 7)**
- ADA + MTX had a higher net benefit than MTX alone for both populations across all 1-way sensitivity analysis scenarios **(Figures 6 and 7)**

### Figure 6. Parameters Affecting Incremental NHB of MTX Alone vs. ADA + MTX for the MTX-Naïve Population




ACR, American College of Rheumatology; ADA, adalimumab; AE, adverse event; HAQ, Health Assessment Questionnaire; LOE, lack of efficacy; MTX, methotrexate; NHB, net health benefit; RR, relative risk.

### Figure 7. Parameters Affecting Incremental NHB of MTX Alone vs. ADA + MTX for the DMARD-Failure Population




ACR, American College of Rheumatology; ADA, adalimumab; AE, adverse event; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; LOE, lack of efficacy; MTX, methotrexate; NHB, net health benefit; RR, relative risk.

### Strengths and Limitations of Benefit-Risk Model

- Strengths
  - The model was populated with data that were statistically adjusted for differences in patient populations and were filtered to include only research that satisfies quality standards[5–17]
  - The model used both ACR response rates and HAQ-DI scores and therefore represents RA therapy efficacy and benefit-risk measures that are commonly accepted in the RA and cost-effectiveness literature[18–23]
  - The risks considered in the model represented those AEs that are most commonly measured in clinical trials and appear most often as warnings in prescription information[2–4] for the therapies studied in the model
  - Both benefits and risks were associated with changes in utilities, which allowed the 2 to be compared through a common measure
  - Comprehensive sensitivity analyses were performed utilizing all available data to more fully understand which parameters have the greatest impact on the results
- Limitations
  - Assumptions had to be made around some data, such as the age/sex distribution of the study population, due to the limited availability of these data. However, we believe the results were not affected significantly by these assumptions because they were not seen as significant factors in the 1-way sensitivity analyses
  - The analysis did not include a probabilistic sensitivity analysis (PSA). Due to the large amount of time required for each model run and the large number of runs required to do a PSA, this type of analysis would require such a large amount of time that it is infeasible to carry out. However, we have run a number of sensitivity analyses and have found that results of these analyses are robust

## Conclusions

- To our knowledge, there are no published benefit-risk analyses comparing these RA treatments
- Analysis of treatment-related risks vs. improvements in outcomes in a simulation model revealed that both MTX-naïve and DMARD-failure patients may experience greater net health benefits when treated with a combination of ADA and MTX than when treated with a combination of IFX + MTX or MTX alone

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*Presented at 15th Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research, 3–7 November 2012, Berlin, Germany*