Subcutaneous methotrexate for treating rheumatoid arthritis in Portugal: a cost-utility analysis versus current practice

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Abstract

Aims: This study evaluated the cost-utility of subcutaneous versus oral methotrexate for rheumatoid arthritis (RA) management in Portugal.

Methods: A cost-utility analysis (CUA) was conducted over a lifetime horizon from the Portuguese National Health Service perspective, adapting a model previously published for the United Kingdom. Patients were modelled to transition through lines of therapy including conventional synthetic, followed by biologic and targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs). In the base case, first-line subcutaneous methotrexate was compared with first-line oral methotrexate, while a scenario analysis explored second-line subcutaneous methotrexate use, after failing first-line oral methotrexate. Clinical, quality-of-life, and cost data were sourced from the literature, using Portuguese data where available. Projected costs and benefits were combined in net monetary benefit (NMB) estimates, evaluated against a willingness-to-pay threshold of €50,000 per quality-adjusted life-year (QALY) gained. The robustness of results was explored in sensitivity and scenario analyses.

Results: First-line subcutaneous methotrexate was projected to yield an additional 0.25 life-years and 0.55 QALYs, while reducing total costs by €11,108 over patients' lifetimes, relative to first-line oral methotrexate. Using subcutaneous methotrexate after first-line oral methotrexate was associated with gains in life expectancy (+0.54 life-years) and quality-adjusted life expectancy (+1.19 QALYs), while also reducing projected costs (–€25,892). In both analyses, subcutaneous methotrexate was therefore associated with improved effectiveness and reduced total costs. The corresponding NMBs were €38,821 and €85,485, respectively. Health gains resulted from more patient time spent on active treatment, with improved disease control, and consequently better health-related quality of life and reduced mortality risk. Improved disease control also implied reduced hospitalization costs, with costs further reduced due to delaying, or avoiding, costly biologics, which offset higher subcutaneous methotrexate acquisition costs. Sensitivity and scenario analyses confirmed base case results, including for different later-line biologic treatments, clinical response data, and time horizons.

Conclusions: This CUA evaluated the value-for money of subcutaneous versus oral methotrexate for RA management in Portugal and found that subcutaneous methotrexate is likely a cost-effective strategy, with the potential to reduce healthcare expenditure and improve patient outcomes. These findings support consideration of wider adoption of subcutaneous methotrexate within Portuguese clinical practice.

Keywords: Cost-utility analysis; Health economics; Cost; Methotrexate; Antirheumatic agents; Rheumatoid arthritis; Route of administration; Portugal

Introduction

Rheumatoid arthritis (RA) is a chronic and inflammatory autoimmune disease, which damages joints, cartilage, and bone[1]. Globally, an estimated 17.6 million people lived with RA in 2020[2], including 47,000 in Portugal, while 2023 population data[3] combined with published prevalence data[4] suggest 65,000 adults in Portugal had RA. Mortality associated with RA has declined, but patient numbers are projected to increase in Western Europe due to population ageing and despite limited population growth[2]. The clinical burden of RA is considerable, mainly through damage caused to joints and including pain, functional impairment, and fatigue[1,5], but also otologic manifestations[6], e.g., hearing loss and vertigo, elevated fracture[7] and cardiometabolic comorbidity[8] risk, and depression[9]. The clinical burden reduces patients' quality of life (QoL), which is consistently lower than in reference populations[10–12]. Psychological distress has been identified as a barrier to better QoL, while patients are concerned to maintain independence and autonomy[13].

In addition, RA is costly for healthcare systems and societies. The 2010 societal costs of RA in Portugal were estimated at €120 million, for an estimated 35,000 patients[14] – more recent estimates were not identified but contemporary estimates are likely higher given larger estimated patient populations and healthcare cost inflation. Productivity losses are a notable economic concern as RA is a leading cause of early retirement in Portugal, where, on average, 7 years of active work life are lost to early RA-related retirement relative to retirement for other causes[15]. In the working population with RA, RA-related absenteeism (reported by 40% of those affected) and overall work impairment (46%) are frequent while a significant share of patients does not hold a paid job[11].

Treatment of RA in Portugal is recommended to start with the conventional synthetic disease-modifying antirheumatic drug (csDMARD) methotrexate[16]. This is either parenteral or orally administered methotrexate, to be started at 10–15 mg/week and escalated, if feasible, by 5 mg/week every 2–4 weeks to 25 mg/week, with parenteral administration not only a first-line option but also to be considered if oral methotrexate is inadequate or not tolerated. Portuguese guidance further states that methotrexate monotherapy is preferred over combination with other conventional DMARDs and that methotrexate should anchor treatment in any such combination[16]. If the treatment target cannot be achieved with optimal csDMARD therapy, therapy should be escalated to biological (bDMARD) or targeted synthetic (tsDMARD) treatments such as tumour necrosis factor inhibitor (TNFi) and Janus kinase inhibitors (JAKi)[17].

The use of subcutaneous and oral methotrexate was investigated for Portugal in the Utilization of Metoject® in RA (UMAR) study[18]. In UMAR, subcutaneous methotrexate demonstrated good tolerability, compared with oral methotrexate, and was associated with good persistence when used after failure of or intolerance to oral methotrexate. The UMAR study group explicitly noted the potential of subcutaneous methotrexate to delay or avoid costly biologic treatment. This argument was recently projected to hold for the United Kingdom (UK), where the improved effectiveness and tolerability of subcutaneous over oral methotrexate[19–21] translated into long-term cost savings and quality-adjusted life expectancy (QALE) benefits when using subcutaneous methotrexate as second-line treatment[22]. The present article adapts this cost-utility analysis (CUA) for Portugal, to assess the value for money of subcutaneous methotrexate in RA treatment pathways.

Material and methods

Model description

The model was developed from findings of comprehensive literature searches for a comparison of subcutaneous and oral methotrexate in the UK[22], to which we refer readers for full model details. Briefly, the model combined a short-term, upfront decision tree with a longer-term Markov model, to project a simulated patient cohort progressing through lines of therapy in 3-month cycles (**Figure 1**). The model captured treatment efficacy through initial response and longer-term disease progression. Initial response to first-line treatment was modelled using a decision tree. Subsequent disease progression was captured through transition probabilities in the Markov component, reflecting the cyclical risk of treatment discontinuation or failure. Patients achieving a 'good' response in the decision tree entered the Markov model on first-line treatment, whereas those with a 'poor' response transitioned to second-line treatment upon entry to the Markov model. Subsequent states in the Markov model were defined by position in the treatment sequence (see **Figure 1** and next subsection), up to the final active treatment line, which, for present purposes, we also refer to as best supportive care (BSC). While on active therapy, patients were at risk of treatment-specific adverse events (AEs), applied as per-cycle rates.

For the present analysis, the model and input data were adapted to reflect clinical practice in Portugal. This included, as detailed in subsequent sections, modelling treatment sequences reflective of Portuguese clinical practice, using population/demographic, clinical, and QoL data derived from Portuguese patient cohorts, where available, and employing resource use estimates and costs specific to Portugal. While the core structure of the model remained

consistent with the UK analysis[22], a dynamic time component was introduced within the decision tree. Specifically, the decision tree's time horizon was extended beyond 3 months, reflecting preferred response assessment measures in the Portuguese setting and enabling the model to capture treatment responses over an appropriate period.

The CUA was conducted from a Portuguese National Health Service perspective and, in line with guidance issued by INFARMED[23], over patients' lifetime. Costs and consequences were discounted at 4% per year. Incremental cost-utility ratios (ICURs) and net monetary benefits (NMBs) were assessed against willingness-to-pay (WTP) threshold of €50,000 per QALY gained, i.e., slightly below the mid-point of the INFARMED-recommended WTP threshold range from €10,000 to €100,000 per QALY gained (with cost-effectiveness also estimated at the endpoints of this interval).

Treatment sequencing

Portuguese guidance[16,17,24] recommends a stepwise treatment sequence including csDMARDs as well as b/tsDMARDs, as discussed above. In the model, patients failing all prior treatments were assumed to receive a bDMARD in combination with background csDMARDs as BSC. Based on clinical expert opinion, concomitant supportive therapies were assumed to be required alongside conventional treatment. Corticosteroids were included in the first-line setting as short-term bridging therapy to provide rapid disease control while awaiting the onset of action of csDMARDs. Folic acid was assumed to be administered alongside methotrexate-containing regimens across all treatment lines to mitigate treatment-related toxicity and improve tolerability, thereby supporting treatment persistence.

Given clinical discretion at each treatment line, a conservative assumption was applied whereby the lowest-cost option within each treatment class was selected for second- and third-line therapies as well as for BSC. Specifically, the comparator pathway reflecting common Portuguese practice as determined based on clinical practice guidance and expert opinion,[17,25–29] was modelled as comprising first-line oral methotrexate, second-line adalimumab with methotrexate, third-line tofacitinib with methotrexate, and tocilizumab with methotrexate as BSC (**Figure 2**).

The alternative treatment pathway incorporated subcutaneous methotrexate. In the base case, subcutaneous replaced oral methotrexate as first-line treatment, followed by subsequent treatments as per current practice (**Figure 2**). An additional positioning scenario was also explored, in which subcutaneous methotrexate was introduced in the second line. In this scenario, the pathway comprised oral methotrexate in the first line, subcutaneous methotrexate

in the second line, followed by subsequent treatments as per current practice, shifted forward by one line (**Figure 2**).

An equal split between oral and subcutaneous methotrexate as concomitant therapy in later-line treatment was assumed for costing. In practice, patients typically continue their previous administration route; however, due to limited route-specific efficacy data in later lines, applying cost differentials in the absence of demonstrated clinical differences was considered inappropriate. The impact of maintaining the previously used administration route on costs was explored in scenario analyses across both positioning scenarios of subcutaneous methotrexate.

Patient cohort and characteristics

Baseline patient characteristics included age, gender, weight, and Health Assessment Questionnaire (HAQ) scores (Table S I). Mean age was 55.9 years, with 87% of the modelled cohort assumed to be women, based on the UMAR study[18]. Body weight estimates for women and men were sourced from Portuguese National health survey data from 2019[30], as no RA-specific weight data were identified, and weighted by the share of women and men in the modelled cohort, yielding a mean baseline weight of 66.9 kg. The baseline HAQ score was 1.25, from a cross-sectional study in Portugal[12].

Clinical inputs: response, transition probabilities, mortality

Based on clinical expert opinion, the most appropriate measure of treatment response in Portugal was deemed to be the Disease Activity Score 28 (DAS28). Initial response rates were defined as the proportion of patients achieving DAS28 remission at 12 months, sourced from a study evaluating the comparative effectiveness of oral versus subcutaneous methotrexate in early RA[31]. These were 51% for subcutaneous and 44% for oral methotrexate, with the decision tree component modelled over a 12-month time horizon to align with the source data.

Transition probabilities were derived from published data, with an exponential distribution assumed to calculate per-cycle values (Table S I). Probabilities of transitioning from oral or subcutaneous methotrexate to subsequent therapy were sourced from the Canadian Early Arthritis Cohort (CATCH) and UMAR studies, respectively[31,18]. These probabilities also accounted for differential treatment adherence. Transition probabilities for later-line therapy, including further csDMARDs and bDMARDs, were obtained from published observational and register studies[32,33].

Modelling of mortality and AEs followed the approach taken in the UK analysis[22]. Briefly, for mortality, Portuguese lifetables for the general population[3] were adjusted, for each age group and Markov state, based on projected HAQ, using a published algorithm[34]. For AEs, the five most frequent AEs reported for oral (nausea, abdominal pain, dyspepsia, nasopharyngitis, diarrhoea)

and subcutaneous (same as for oral methotrexate, except loss of appetite replacing diarrhoea) methotrexate in a clinical trial[35] were included. The same approach was taken for later-line therapies, again relying on published data[36,37].

QoL

Treatment effects on patient QoL were modelled using HAQ scores mapped to EQ-5D utility scores. When initiating a new treatment, i.e., entering a different Markov state in the model, an effect on HAQ was accounted for, based on published treatment-related HAQ data (Table S II)[31,38,39]. A marked deterioration in HAQ, and therefore QoL, was assumed for transitioning into BSC, reflecting patients having exhausted treatment options and receiving final-line therapy with limited expected clinical benefit. The HAQ score in each Markov state was mapped to utility scores based on a linear regression developed from Spanish data[40], used previously for analyses concerning Portuguese settings[41]. The QoL impact was set to zero for all AEs, reflecting their low severity, in line with prior health technology assessment (HTA)[42].

Costs and resource use

The model accounted for costs related to treatment acquisition and administration, hospitalization, and disease monitoring, which were applied, as appropriate, in each cycle. Treatment acquisition costs were applied per cycle and calculated based on unit price, strength, dose, and administration frequency (**Table I**). Drug acquisition costs were based on list prices from the National Catalogue of Prices, with dosing schedules sourced from the European Medicines Agency.

One-off treatment initiation costs were also included to capture training-related costs. Based on expert opinion, subcutaneous treatment was assumed to require, on average, two 30-minute, nurse-led contact sessions (before start of treatment for training and after the first month to review laboratory results). The training was costed based on Diário da República-published salary bands for nurses[43] and a 35-hour working week.

Hospitalization costs were determined from 2025 Portuguese Morbidity and Mortality data[44] and diagnosis-related groups (GDH)[45,46]. Morbidity data were used to calculate mean length of stay for musculoskeletal and connective tissue disorders (5.7 days; more fine-grained indication data not available), to which the lowest-severity per-diem cost of GDH351 (€350.29) from Portaria n.º254/2018[45,46] was applied. These values were scaled to HAQ bands as defined previously in HTA[42], to reflect the hospitalization cost effect of more severe disease. For this purpose, multipliers for each HAQ band relative to the least severe HAQ band (0.0 to <0.5) were derived from UK HTA data[42] and applied to the above cost, which was then scaled to the model's

cycle length. This yielded per-cycle estimates of hospitalization costs of €21.8 for HAQ values from 0.0 to <0.5, €13.4 for 0.5 to <1.0, €47.5 for 1.0 to <1.5, €68.2 for 1.5 to <2.0, €162.3 for 2.0 to <2.5, and €350.1 for 2.5 and above.

Costs associated with monitoring, screening, and healthcare resource use were included in the model, with unit costs sourced from GDH[46] (Table S III). Key elements of routine monitoring were assumed to comprise full blood count, creatinine and often also electrolytes, liver function tests, C-reactive protein, urinalysis, and once-yearly lipid profile. Pre-treatment screening included chest X-ray, tuberculosis screening (TB spot test), hepatitis B/C serology, antinuclear antibody, anti-dsDNA, and HIV testing. Healthcare resource use included general practitioner and specialist visits. The utilization of each component was stratified by treatment type and phase, with costs applied at treatment initiation and cyclically while on treatment (Table S IV).

Given low AE severity and based on expert opinion, no AE costs were included in the base case. The inclusion of a uniform cost applied across all AEs was explored in a scenario analysis.

Sensitivity and scenario analyses

Scenario analyses were conducted to explore uncertainty across key structural and input assumptions (Table S I). These included alternative treatment cost assumptions (e.g. switching TNFi and JAKi comparators, removal of treatment in BSC, and concomitant MTX administration route)[24], variations in clinical inputs and treatment effect assumptions, including alternative definitions and timing of initial response using DAS28[31] and ACR20[19], different HAQ-to-utility and HAQ-to-mortality mapping algorithms, and alternative baseline HAQ values, and changes to cost inputs, including hospitalization, AE, and training time costs. In addition, methodological assumptions were varied, including alternative time horizons and discount rates, to assess the impact of long-term extrapolation and discounting on model outcomes.

Sensitivity analyses were also conducted. One-way sensitivity analysis (OWSA) varied each input by ±15% to assess its impact on outcomes, with results visualized in a tornado plot. Probabilistic sensitivity analysis (PSA) used 10,000 iterations to quantify overall uncertainty and estimate the probability of cost-effectiveness.

Ethics

No studies with human participants were performed by any of the authors. Ethics committee approval was not required.

Results

Base case and sensitivity analyses

When subcutaneous methotrexate was introduced as first-line treatment (base case), greater health benefits and reduced costs were projected relative to first-line oral methotrexate, with gains of +0.55 QALYs and +0.25 life-years, alongside cost savings of €11,108. This resulted in an NMB of €38,821. Similarly, when subcutaneous methotrexate was introduced as a second-line treatment following oral MTX, incremental benefits were observed versus not using subcutaneous methotrexate, with gains of +1.19 QALYs and +0.54 life-years, and cost savings of €25,892, yielding an NMB of €85,485. In both scenarios, the sequences including subcutaneous methotrexate dominated comparator sequences, i.e., were less costly and more effective. Including subcutaneous methotrexate increased treatment costs within earlier lines of therapy, which were offset by downstream cost savings driven by delayed, reduced use of biologic therapies (Figures S1 and 2). Additional savings were observed in hospitalization, reflecting improved disease control and delayed progression to BSC, which was associated with higher HAQ scores and increased healthcare resource use. Health gains in both scenarios were primarily driven by patients spending more time on active treatment with improved disease control, resulting in lower HAQ scores, improved health-related quality of life, and reduced mortality risk.

A PSA was conducted to assess overall parameter uncertainty (

Figure 3) for the base case positioning of subcutaneous methotrexate. Across 10,000 iterations, the subcutaneous methotrexate pathway was associated with a mean QALE gain of 0.14 QALYs and a mean cost saving of €6,576 compared with the comparator, resulting in a mean NMB of €13,560. The intervention was therefore dominant on average, while the PSA reflected considerable parameter uncertainty. At a WTP threshold of €50,000 per QALY, the probability of subcutaneous methotrexate being cost-effective was 81%, while the corresponding probabilities were 68% and 89% at WTP thresholds of €10,000 and €100,000 per QALY gained, respectively, supporting the robustness of the base case findings under parameter uncertainty.

In OWSA (**Figure 4**), the NMB was positive across all scenarios, indicating that the subcutaneous methotrexate pathway remained cost-effective. Results were most sensitive to transition probabilities, particularly those associated with JAKi, subcutaneous methotrexate, and TNFi treatment lines, which produced the largest variation in NMB. Additional influential parameters

included baseline age and subcutaneous methotrexate response. Other inputs, including acquisition costs, HAQ impact at treatment initiation, and discounting, had a more moderate impact, while assumptions related to the final active treatment line and body weight had minimal influence. Overall, the findings were robust to variation in key inputs.

Scenario analyses

Several scenario analyses were conducted to assess structural and parameter uncertainty (**Figure 5**, Table S V). Across all scenarios, the pathway including subcutaneous methotrexate remained dominant for both first- and second-line positioning. Results were most sensitive to assumptions relating to time horizon and discounting. Shorter time horizons substantially reduced incremental QALE and cost savings, while removal of discounting increased NMB markedly. Assumptions around initial treatment response and HAQ-to-utility mapping also influenced the magnitude of QALY gains but did not alter the overall conclusion of dominance. Changes to treatment costs and pathway composition had a notable impact on incremental costs. Removing treatment costs in the final active treatment line substantially reduced cost savings, while switching between higher-cost TNFi options increased the magnitude of cost savings. Similarly, variations in JAKi costs and other treatment-related assumptions led to meaningful shifts in incremental costs, although subcutaneous methotrexate remained cost saving in all scenarios. Other assumptions, including hospitalization costs, adverse event costs, subcutaneous methotrexate training time, baseline HAQ, and concomitant MTX administration, had a modest impact on results.

Discussion

This CUA evaluated the long-term health economic impact of subcutaneous methotrexate-focused RA treatment pathways in Portugal. The analysis was based on a previously published model[22], adapted to and conducted from a Portuguese healthcare system perspective. Subcutaneous methotrexate, as either a first- or second-line treatment option, was likely cost-effective at a threshold of €50,000 per QALY. Specifically, in both treatment lines, using subcutaneous methotrexate was projected to increase life expectancy and QALE while reducing overall costs relative to common practice based solely on oral methotrexate. The former were driven by longer time on active treatment and reduced HAQ scores, resulting in improved QoL and reduced mortality. The latter were identified despite higher acquisition costs for subcutaneous methotrexate due to reducing and delaying the need for costly biologics. Results showed variation in response to varying inputs and different scenarios, including to discount

rates, time horizons, and biologic treatment costs, but were robust overall and consistent in projecting subcutaneous methotrexate to be good value for money from a Portuguese healthcare system perspective.

To our knowledge, this is the first published study modelling the expected clinical and economic consequences of increased utilization of subcutaneous methotrexate for RA treatment in Portugal. Results, as discussed above, mirrored those obtained for the UK[22]. Like the UK analysis, the present CUA for Portugal had a number of limitations that need to be considered when interpreting results. These included a lack of data specific to Portugal in particular for clinical data, with no pertinent data, Portuguese or otherwise, identified for some later-line transition probabilities. Consequently, modelling treatment trajectories was simplified by assuming these probabilities to be constant across time on treatment and to be independent of treatment line. These assumptions abstracted from the clinical complexity of RA and will have to be evaluated if appropriate data become available, with previous modelling, however, suggesting their impact to be limited[22]. In addition, a wide array of sensitivity and scenario analyses was conducted pertaining to both modelling assumptions and input data, including where no Portuguese data were available, had to be derived from different sources, such as for severity-specific hospitalization costs, or were based on expert consultation, which has a residual risk of subjective bias and is of comparatively reduced reproducibility. These analyses yielded robust and consistent results, implying a low likelihood for modelling results to depend strongly on any specific data source although significant parameter uncertainty was evident from PSA. While not changing overall results and conclusions, this reflects the noticeable uncertainty in some model inputs, including treatment effects for which future head-to-head studies[47] of subcutaneous and oral methotrexate will hopefully provide more robust comparative evidence. It should also be noted that an equal split between methotrexate administration routes was assumed in later-line therapy. This assumption likely diverged from routine care, in which patients would probably continue their previous route of administration unless there was a cause for switching[48]. However, this assumption was required to allow for a fair comparison of treatment routes as, in the absence of route-specific effectiveness data for later line-therapy, the use of differential acquisition costs without differential effectiveness estimates would have biased the CUA. During model development, consultation with clinical experts also identified a significant range of treatment choices and combinations permitted by published guidance and recommendations[16,17,24]. The modelled use of adalimumab as the first and tofacitinib as the second post-csDMARD option was deemed plausible but represented only one of multiple treatment options. Alternatives were explored in scenario analyses and found to have only

limited impact on results. Still, as with any health economic model, projecting lifetime outcomes from relatively short-term data, e.g. on the comparative performance of subcutaneous and oral methotrexate[18,31], and combining data and assumptions from different sources, e.g., using HAQ-related hospitalization multipliers derived from UK data, implies noticeable uncertainty.[49,50] While addressed in scenario and sensitivity analyses, this uncertainty must be considered in any clinical and economic decision-making based on present results.

The health economic projections presented in this paper should be considered within the wider context of RA care in Portugal, where economic and clinical concerns suggest some room for improvement. Some of these concerns pertain specifically to b/tsDMARDs, including their infrequent use in combination with methotrexate (as would be recommended) – only about 30% of patients receiving biological therapy receive methotrexate[51]. Furthermore, as noted by the Portuguese Society of Rheumatology[17], the high cost of bDMARDs/tsDMARDs exerts a substantial burden on the healthcare budget although it must be acknowledged that biologic use appears to be modest in Portugal relative to other high-income countries[52]. There are additional concerns regarding bDMARD side effects, including severe infections such as blood stream infections in the case of TNFi (with no association of blood stream infections seen for concomitant immunosuppressive medication[53]), which occur in up to 4.2% of patients in Portugal and of which nearly half lead to discontinuation of the first bDMARD within 6 months[54]. Adverse events associated with bDMARDs also disproportionally affect vulnerable patient groups such as patients with chronic kidney disease or prior orthopaedic surgery and elderly patients[25].

Delaying and reducing the need for escalation to bDMARDs/tsDMARDs, as demonstrated in the present CUA, would likely improve both clinical and economic outcomes. An additional mechanism to achieve this goal would be more timely RA diagnosis in early arthritis clinics, for which not only clinical improvements were reported at a large tertiary centre in Portugal[55], but also that no patient required bDMARDs/tsDMARDs in the first 12 months (for similar findings of reduced biologic need and consequently lower healthcare costs resulting from earlier access to specialist care, see Licker *et al.*[56]). Early diagnosis could, over time, also reduce early retirement, for which delayed diagnosis is a risk factor[15]. Similarly, non-surgical, non-pharmacological approaches to improve patients' happiness and QoL have been suggested for Portugal, including pain relief, increasing exercise, and extending psychological support[57,58]. Some of these suggestions may be more easily implementable than others but most would likely require substantial efforts to restructure entire care pathways and scale up nationwide, e.g., as currently only 16% of patients are seen within the recommended 6 weeks of symptom onset[55]. It is

therefore plausible that improvements to pharmacological interventions across the treatment pathway, especially those increasing treatment effectiveness while meeting patients' informational, self-efficacy, and convenience needs[59], will form a cornerstone for optimizing RA treatment for the foreseeable future, including in Portugal.

Conclusion

This CUA demonstrated that the extended use of subcutaneous methotrexate in RA, both as a first-line treatment and after failed first-line oral methotrexate, would likely represent good value for money from the perspective of the Portuguese healthcare system. Over patients' lifetimes, treatment pathways based on subcutaneous methotrexate would improve life expectancy and QALE and reduce costs relative to current, oral methotrexate-focused practice. These benefits resulted from the higher effectiveness of subcutaneous versus oral methotrexate and the resulting possibility to delay and reduce the need to escalate therapy to bDMARDs or tsDMARDs. While model limitations and the uncertainty inherent into any long-term projections need to be considered, these results suggest that extending the availability and use of subcutaneous methotrexate in Portuguese clinical practice could contribute to alleviating the clinical and economic burden of RA.

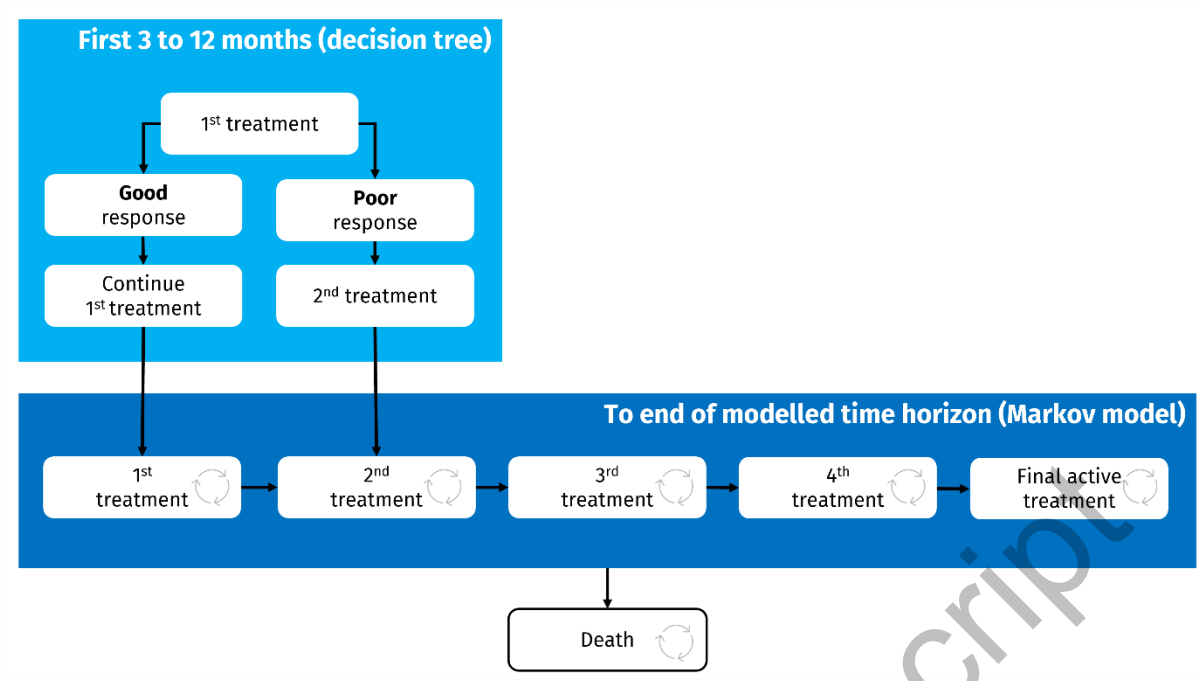
Tables and Figures

Table I - Treatment cost inputs

Treatment compound	Dose per administration (mg)	Acquisition cost (€) per administrated dose	Weekly frequency of administration	Source (in addition to National Catalogue)
Subcutaneous methotrexate	25	23.48	1	Duarte *et al.*[16]
Oral methotrexate	25	0.96	1	Duarte *et al.*[16]
Tumour necrosis factor (adalimumab)	40	113.00	0.5	Capell *et al.*[60]; SmPC[61]
Janus kinase inhibitor (tofacitinib)	5	5.90	14	SmPC[62]
Best supportive care (tocilizumab)	534.93*	419.09	0.25	SmPC[63]
Folic acid	10	0.15	1	-
Corticosteroids	10	0.07	7	-

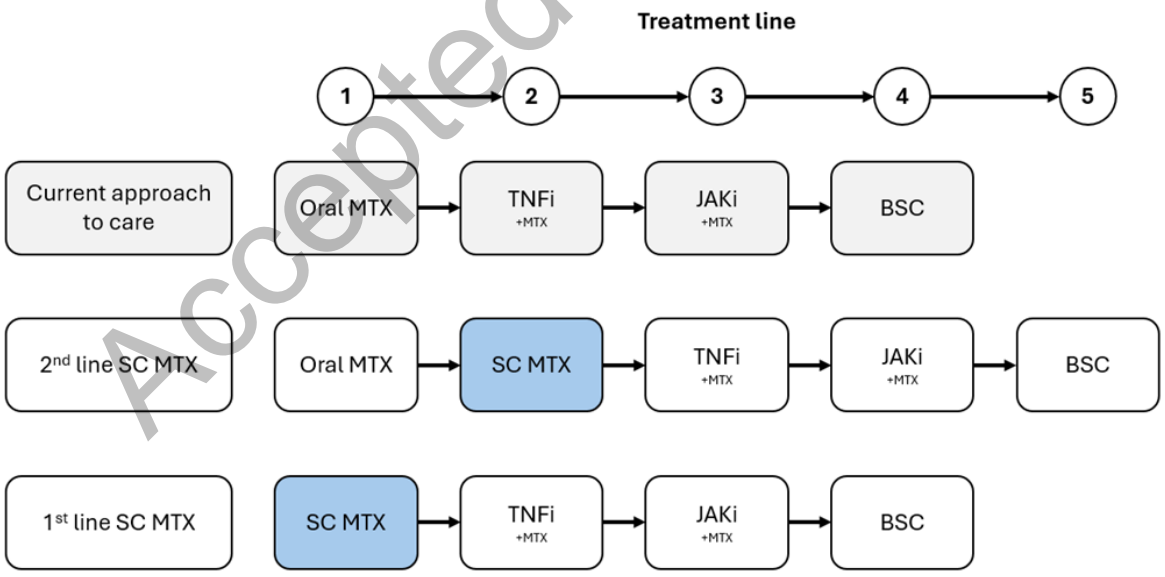
EMA, European Medical Agency; SmPC, Summary of Product Characteristics. *Body weight (for dosing) as 66.87 kg[30]

Figure 1 - Model schematic



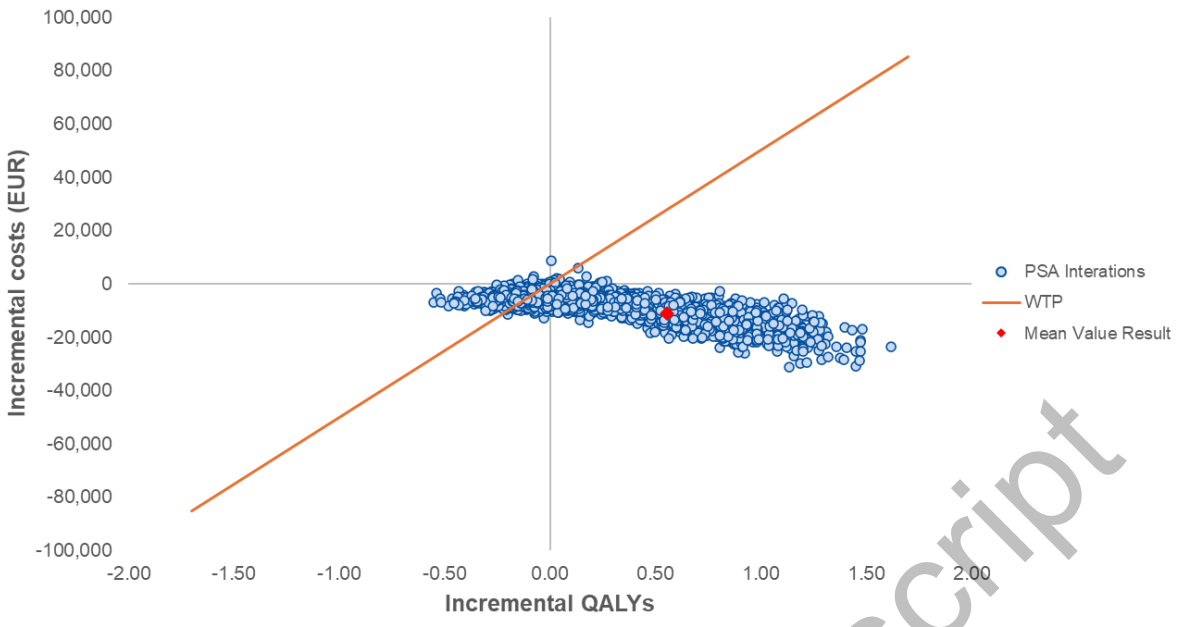
Circular arrows indicate states in which multiple cycles can be spent.

Figure 2 - Modelled treatment scenarios



BSC, Best Supportive Care; JAKi, Janus Kinase Inhibitor; MTX, Methotrexate; TNFi, Tumour Necrosis Factor Inhibitor.

Figure 3 - PSA scatter plot



PSA, Probabilistic sensitivity analysis; QALYs, Quality-adjusted life-years.

Figure 4 - One-way sensitivity analysis tornado plot

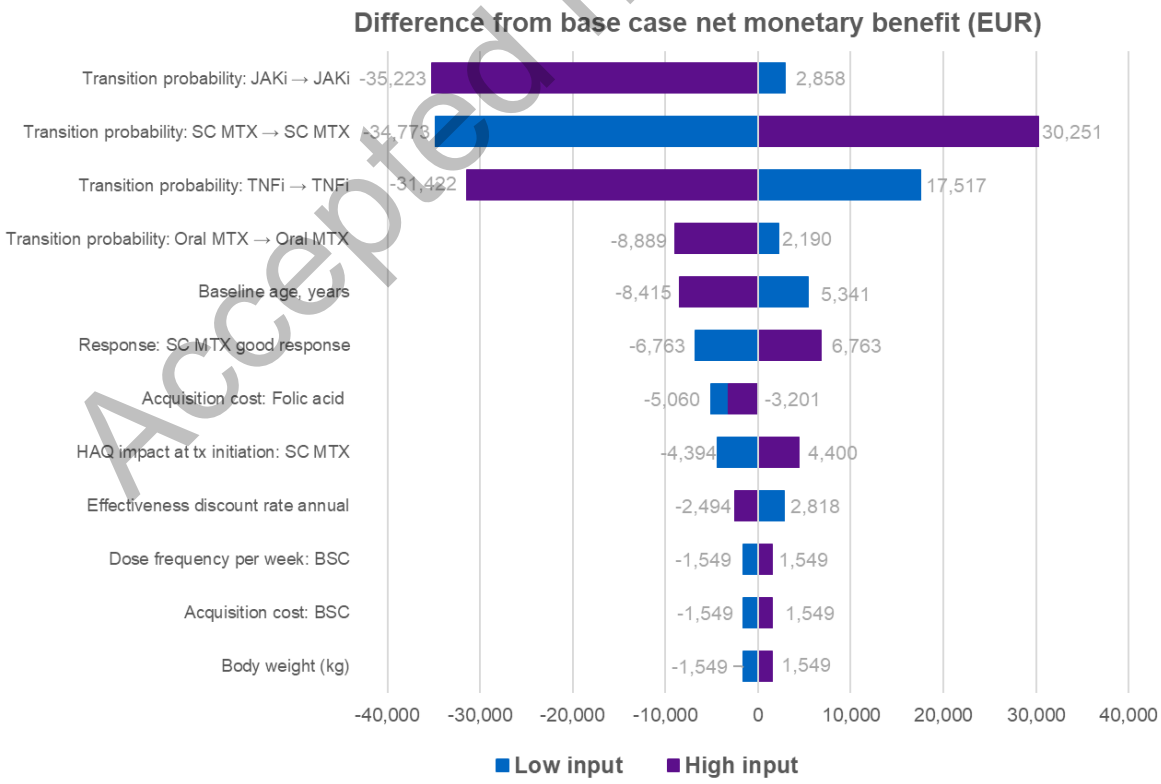
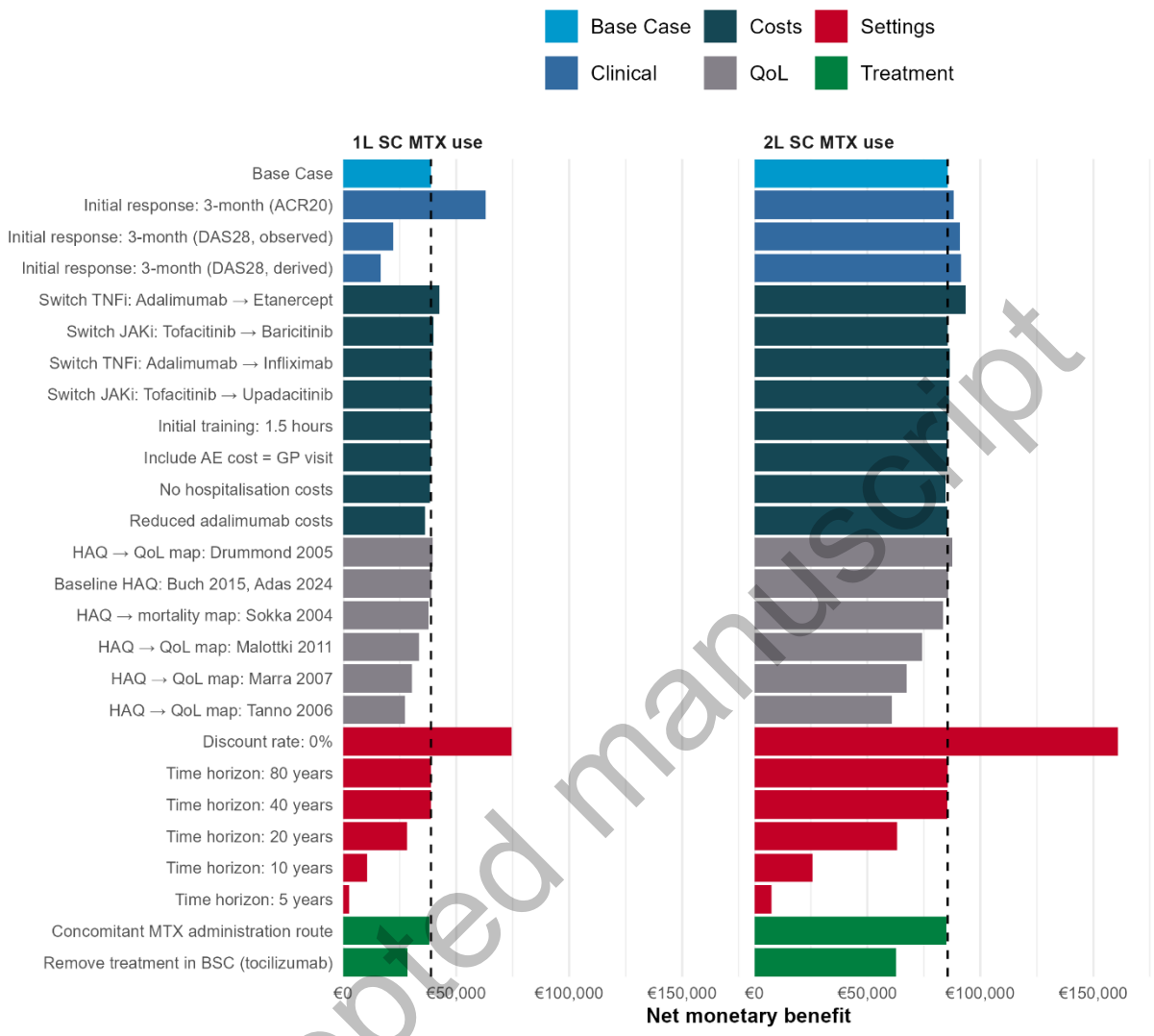


Figure 5 - Results from scenario analyses



ACR, American College of Rheumatology; AE, Adverse Event; BSC, Best Supportive Care; DAS, Disease Activity Score; GP, General Practitioner; HAQ, Health Assessment Questionnaire; JAKi, Janus Kinase Inhibitor; MTX, Methotrexate; QoL, Quality of Life; TNFi, Tumour Necrosis Factor Inhibitor. See Table S I for additional details, including references.

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Supplementary Material

Table S I - Overview of base case and scenario analyses

Scenario group	Base case	Scenario
Treatment costing	TNFi for costing is adalimumab	• TNFi for costing is etanercept • TNFi for costing is infliximab
Treatment costing	JAKi for costing is tofacitinib	• JAKi for costing is baricitinib • JAKi for costing is upadacitinib
BSC treatment composition	BSC includes tocilizumab+concomitant MTX+folic acid	No treatment associated with BSC
Initial treatment response (time horizon and measure)	Initial 12-month response period with DAS response rates (51% subcutaneous methotrexate; 44% oral MTX)[1]	• Initial 3-month response period with DAS response rates (27% and 21%)[1] • Initial 3-month response period with DAS response rates (21% and 15%; derived from 9-month data) [1] • Initial 3-month response period with ACR20 response rates (78% and 64%)[2]
HAQ to utility mapping	Carreño *et al.*[3]	• Tanno *et al.*[4] • Drummond *et al.*[5] • Malottki *et al.*[6] • Marra *et al.*[7] • Sokka *et al.*[8]
Hospitalization costs	Hospitalization costs increase with HAQ	Zero hospitalization costs
Subcutaneous treatment administration costs	1-hour training	1.5-hour training
Time horizon (years)	50	5, 10, 20, 40, 80
Discounting	4% discount rate for costs and benefits	0% discount rate for costs and benefits
Adverse event costs	No costs associated with AEs	Cost of each AE equivalent to a general practitioner visit
Baseline HAQ	Rosa-Gonçalves *et al.*[9] (1.25)	Buch *et al.*[10], Adas *et al.*[11] (1.20)

ACR, American College of Rheumatology; AE; Adverse Event; BSC, Best Supportive Care; HAQ, Health Assessment Questionnaire; JAKi, Janus Kinase Inhibitor; MTX; Methotrexate; TNFi, Tumor Necrosis Factor Inhibitor.

Table S II - Clinical inputs

Treatment	Input	Note
Transition probabilities (cyclical probability of remaining on treatment)‡		
Subcutaneous methotrexate[12]	0.98	-
Oral methotrexate[1,12]	0.81	Scaling from CATCH study[1], applied to efficacy of subcutaneous methotrexate from UMAR study[12]
TNFi[13]	0.98	-
JAKi[14]	0.89	-
HAQ impact on quality of life at treatment initiation†		
Subcutaneous methotrexate[1,15]	−0.34	-
Oral methotrexate[15]	−0.32	-
TNFi and methotrexate	−0.32	Assumption (same as oral MTX)
JAKi and methotrexate	−0.50	Assumption
Best supportive care[16]	0.50	Assumption that patients are 'much worse'

CATCH, Canadian Early Arthritis Cohort; HAQ, Health Assessment Questionnaire; JAKi, Janus Kinase Inhibitor; TNFi, Tumor Necrosis Factor Inhibitor; UMAR, Utilization of Metoject® in RA[12].
‡Cyclical transition probabilities to the next line of treatment were calculated as 1 minus the probability of remaining on the current treatment. All cyclical probabilities were derived assuming an exponential distribution. †HAQ impacts applied additive to baseline at treatment initiation and maintained while on treatment. Also see Tucker *et al.*[17] for further details

Table S III - Cyclical resource costs

Test	Cost (€)	Source
Chest X-ray	5.00	Portaria n.º 254/2018[18] code 10405
Full blood count	4.70	Portaria n.º 254/2018[18] code 24209
Urea & electrolyte	1.30	Portaria n.º 254/2018[18] code 22949
Liver function	9.20	Portaria n.º 254/2018[18] codes 21140 (albumin), 21935 (alkaline phosphatase), 22035 (gamma-glutamyl-transferase), 21217 (ALT), 21220 (AST), 22679 (total protein), 21340 (bilirubin)
C-reactive protein	3.17	Portaria n.º 254/2018[18] code 22669
Urinalysis	0.70	Portaria n.º 254/2018[18] code 22959
Tuberculosis spot	39.90	Portaria n.º 254/2018[18] code 26003
Hepatitis serology	42.20	Portaria n.º 254/2018[18] codes 26069, 26527, 26067
Antinuclear antibody	13.17	Portaria n.º 254/2018[18] code 25057
Anti-double standard desoxyribonucleic acid	9.77	Portaria n.º 254/2018[18] code 25023
Uric acid	1.30	Portaria n.º 254/2018[18] code 21101

Test	Cost (€)	Source
Lipids	6.00	Portaria n.º 254/2018[18] codes 21539, 21545, 22920
Acquired immunodeficiency syndrome	40.80	Portaria n.º 254/2018[18] codes 26328
General practitioner visit	34.10	Portaria n.º 207/2017[19] Artigo 15.° (first consultation - subsequent consultations are €31.00)
Specialist visit	34.10	Portaria n.º 207/2017[19] Artigo 15.° (first consultation - subsequent consultations are €31.00)

Table S - IV Cyclical resource use for disease monitoring: treatment initiation

Test	SC MTX	Oral MTX	TNFi	JAKi	BSC
Treatment initiation					
Chest X-ray	1	1	1	1	0
Full blood count	1	1	1	1	0
Creatinine & electrolyte	1	1	1	1	0
Liver function	1	1	1	1	0
C-reactive protein	1	1	1	1	0
Urinalysis	1	1	1	1	0
Tuberculosis spot	1	1	1	1	0
Hepatitis B/C serology	1	1	1	1	0
Antinuclear antibody	1	1	1	1	0
Anti-double stranded desoxyribonucleic acid	0	0	1	1	0
Uric acid	1	1	1	1	0
Lipids	1	1	1	1	0
Acquired immunodeficiency syndrome	0	0	1	1	0
General practitioner visit	0	0	0	0	0
Specialist visit	1.5	1.5	1.5	1.5	1.5
Post-treatment initiation					
Chest X-ray	0	0	0	0	0
Full blood count	0.75	0.75	0.75	0.75	0.75
Creatinine & electrolyte	0.75	0.75	0.75	0.75	0.75
Liver function	0.75	0.75	0.75	0.75	0.75
C-reactive protein	0.75	0.75	0.75	0.75	0.75
Urinalysis	0.75	0.75	0.75	0.75	0.75
Tuberculosis spot	0.75	0.75	0.75	0.75	0.75
Hepatitis B/C serology	0	0	0	0	0
Antinuclear antibody	0	0	0	0	0
Anti-double stranded desoxyribonucleic acid	0.75	0.75	0.75	0.75	0.75
Uric acid	0.75	0.75	0.75	0.75	0.75
Lipids	0.75	0.75	0.75	0.75	0.75
Acquired immunodeficiency syndrome	0	0	0	0	0
General practitioner visit	0	0	0	0	0
Specialist visit	0.75	0.75	0.75	0.75	0.75

BSC, Best Supportive Care; JAKi, Janus Kinase Inhibitor; MTX; Methotrexate; SC, Subcutaneous; TNFi, Tumor Necrosis Factor.
Estimates derived from expert elicitation.

Table S V - Results for scenario analyses

NMB (€)	ICUR (€/QALY gained)	Outcome	Intervention	Comparator	Increment
1L SC MTX use - Base Case					
38,821	-20,042	LY	26.61	26.36	0.25
		QALY	9.60	9.05	0.55
		Costs (€)	58,743.24	69,851.55	-11,108.32
1L SC MTX use - Initial response: 3-month (DAS28, derived)					
16,649	-19,535	LY	26.42	26.31	0.10
		QALY	9.12	8.88	0.24
		Costs (€)	70,348.76	75,026.23	-4,677.47
1L SC MTX use - Initial response: 3-month (DAS28, observed)					
22,075	-19,834	LY	26.45	26.32	0.14
		QALY	9.20	8.89	0.32
		Costs (€)	68,434.69	74,704.29	-6,269.60
1L SC MTX use - Switch JAKi: Tofacitinib → Upadacitinib					
39,145	-20,651	LY	26.61	26.36	0.25
		QALY	9.61	9.05	0.55
		Costs (€)	59,802.12	71,244.18	-11,442.05
1L SC MTX use - Switch TNFi: Adalimumab → Infliximab					
39,306	-20,942	LY	26.61	26.36	0.25
		QALY	9.61	9.05	0.55
		Costs (€)	60,372.95	71,975.89	-11,602.93
1L SC MTX use - Switch JAKi: Tofacitinib → Baricitinib					
39,817	-21,864	LY	26.61	26.36	0.25
		QALY	9.61	9.05	0.55
		Costs (€)	61,933.52	74,047.48	-12,113.95
1L SC MTX use - Switch TNFi: Adalimumab → Etanercept					
42,478	-26,666	LY	26.61	26.36	0.25
		QALY	9.61	9.05	0.55
		Costs (€)	70,822.82	85,597.64	-14,774.82
1L SC MTX use - Initial response: 3-month (ACR20)					
63,057	-20,452	LY	26.73	26.34	0.39
		QALY	9.86	8.97	0.90
		Costs (€)	54,024.07	72,329.38	-18,305.31
1L SC MTX use - Reduced adalimumab costs					
36,138	-14,532	LY	26.61	26.36	0.25
		QALY	9.61	9.05	0.56
		Costs (€)	48,959.00	57,097.00	-8,138.00
1L SC MTX use - No hospitalisation costs					
38,402	-19,310	LY	26.61	26.36	0.25
		QALY	9.61	9.05	0.55
		Costs (€)	56,870.72	67,569.46	-10,698.75
1L SC MTX use - Include AE cost = GP visit					

NMB (€)	ICUR (€/QALY gained)	Outcome	Intervention	Comparator	Increment
38,729	-19,901	LY	26.61	26.36	0.25
		QALY	9.61	9.05	0.55
		Costs (€)	59,017.53	70,043.91	-11,026.38
1L SC MTX use - Initial training: 1.5 hours					
38,808	-20,044	LY	26.61	26.36	0.25
		QALY	9.61	9.05	0.55
		Costs (€)	58,746.72	69,852.03	-11,105.31
1L SC MTX use - HAQ → QoL map: Tanno 2006					
27,311	-34,281	LY	26.61	26.36	0.25
		QALY	8.71	8.39	0.32
		Costs (€)	58,743.65	69,852.03	-11,108.38
1L SC MTX use - HAQ → QoL map: Marra 2007					
30,406	-28,782	LY	26.61	26.36	0.25
		QALY	10.53	10.15	0.39
		Costs (€)	58,743.65	69,852.03	-11,108.38
1L SC MTX use - HAQ → QoL map: Malottki 2011					
33,505	-24,799	LY	26.61	26.36	0.25
		QALY	8.29	7.84	0.45
		Costs (€)	58,743.65	69,852.03	-11,108.38
1L SC MTX use - HAQ → mortality map: Sokka 2004					
37,767	-13,451	LY	20.41	19.51	0.89
		QALY	8.36	7.76	0.60
		Costs (€)	45,664.75	53,671.11	-8,006.35
1L SC MTX use - Baseline HAQ: Buch 2015, Adas 2024					
38,976	-19,997	LY	26.71	26.45	0.25
		QALY	9.87	9.31	0.56
		Costs (€)	58,917.94	70,052.48	-11,134.53
1L SC MTX use - HAQ → QoL map: Drummond 2005					
39,749	-19,393	LY	26.61	26.36	0.25
		QALY	7.75	7.18	0.57
		Costs (€)	58,743.65	69,852.03	-11,108.38
1L SC MTX use - Time horizon: 5 years					
2,549	-60,593	LY	4.95	4.95	0.00
		QALY	3.03	3.01	0.02
		Costs (€)	10,415.32	11,812.00	-1,396.68
1L SC MTX use - Time horizon: 10 years					
10,569	-41,271	LY	9.74	9.74	0.00
		QALY	5.30	5.19	0.12
		Costs (€)	22,662.39	27,441.38	-4,778.99
1L SC MTX use - Time horizon: 20 years					
28,154	-25,003	LY	18.55	18.51	0.04
		QALY	8.12	7.75	0.38
		Costs (€)	43,829.04	53,214.62	-9,385.58
1L SC MTX use - Time horizon: 40 years					

NMB (€)	ICUR (€/QALY gained)	Outcome	Intervention	Comparator	Increment
38,795	-20,064	LY	26.60	26.35	0.25
		QALY	9.60	9.05	0.55
		Costs (€)	58,731.76	69,841.38	-11,109.63
1L SC MTX use - Time horizon: 80 years					
38,811	-20,049	LY	26.61	26.36	0.25
		QALY	9.61	9.05	0.55
		Costs (€)	58,743.65	69,852.03	-11,108.38
1L SC MTX use - Discount rate: 0%					
74,394	-16,853	LY	26.61	26.36	0.25
		QALY	15.35	14.24	1.11
		Costs (€)	106,858.13	125,611.81	-18,753.68
1L SC MTX use - Remove treatment in BSC (tocilizumab)					
28,395	-1,248	LY	26.61	26.36	0.25
		QALY	9.61	9.05	0.55
		Costs (€)	32,190.33	32,881.98	-691.65
1L SC MTX use - Concomitant MTX administration route					
38,190	-18,927	LY	26.61	26.36	0.25
		QALY	9.61	9.05	0.55
		Costs (€)	59,004.94	69,491.63	-10,486.69
2L SC MTX use - Base Case					
85,485	-21,724	LY	26.90	26.36	0.54
		QALY	10.24	9.05	1.19
		Costs (€)	43,959.41	69,851.55	-25,892.14
2L SC MTX use - Switch JAKi: Tofacitinib → Baricitinib					
85,463	-21,732	LY	26.90	26.36	0.54
		QALY	10.24	9.05	1.19
		Costs (€)	43,959.75	69,852.03	-25,892.28
2L SC MTX use - Switch JAKi: Tofacitinib → Upadacitinib					
86,183	-22,336	LY	26.90	26.36	0.54
		QALY	10.24	9.05	1.19
		Costs (€)	44,632.37	71,244.18	-26,611.80
2L SC MTX use - Switch TNFi: Adalimumab → Infliximab					
86,529	-22,627	LY	26.90	26.36	0.54
		QALY	10.24	9.05	1.19
		Costs (€)	45,017.75	71,975.89	-26,958.14
2L SC MTX use - Initial response: 3-month (ACR20)					
88,131	-21,681	LY	26.88	26.34	0.54
		QALY	10.20	8.97	1.23
		Costs (€)	45,672.58	72,329.38	-26,656.80
2L SC MTX use - Initial response: 3-month (DAS28, observed)					
91,099	-21,628	LY	26.86	26.32	0.54
		QALY	10.16	8.89	1.27
		Costs (€)	47,196.93	74,704.29	-27,507.36
2L SC MTX use - Initial response: 3-month (DAS28, derived)					

NMB (€)	ICUR (€/QALY gained)	Outcome	Intervention	Comparator	Increment
91,502	-21,621	LY	26.86	26.31	0.54
		QALY	10.15	8.88	1.28
		Costs (€)	47,403.57	75,026.23	-27,622.66
2L SC MTX use - Switch TNFi: Adalimumab → Etanercept					
93,365	-28,365	LY	26.90	26.36	0.54
		QALY	10.24	9.05	1.19
		Costs (€)	51,803.40	85,597.64	-33,794.23
2L SC MTX use - No hospitalisation costs					
84,565	-20,978	LY	26.90	26.36	0.54
		QALY	10.24	9.05	1.19
		Costs (€)	42,575.64	67,569.46	-24,993.83
2L SC MTX use - Include AE cost = GP visit					
85,293	-21,589	LY	26.90	26.36	0.54
		QALY	10.24	9.05	1.19
		Costs (€)	44,322.46	70,043.83	-25,721.36
2L SC MTX use - Reduced adalimumab costs					
85,392	-21,758	LY	26.90	26.36	0.54
		QALY	10.24	9.05	1.19
		Costs (€)	43,960.00	69,852.00	-25,892.00
2L SC MTX use - Initial training: 1.5 hours					
85,461	-21,730	LY	26.90	26.36	0.54
		QALY	10.24	9.05	1.19
		Costs (€)	43,962.62	69,852.03	-25,889.41
2L SC MTX use - HAQ → QoL map: Tanno 2006					
60,723	-37,168	LY	26.90	26.36	0.54
		QALY	9.08	8.39	0.70
		Costs (€)	43,959.75	69,852.03	-25,892.28
2L SC MTX use - HAQ → QoL map: Marra 2007					
67,371	-31,212	LY	26.90	26.36	0.54
		QALY	10.97	10.15	0.83
		Costs (€)	43,959.75	69,852.03	-25,892.28
2L SC MTX use - HAQ → QoL map: Malottki 2011					
74,052	-26,882	LY	26.90	26.36	0.54
		QALY	8.80	7.84	0.96
		Costs (€)	43,959.75	69,852.03	-25,892.28
2L SC MTX use - HAQ → mortality map: Sokka 2004					
83,525	-14,978	LY	21.43	19.51	1.92
		QALY	9.05	7.76	1.29
		Costs (€)	34,417.86	53,671.11	-19,253.25
2L SC MTX use - Baseline HAQ: Buch 2015, Adas 2024					
85,811	-21,672	LY	26.99	26.45	0.54
		QALY	10.51	9.31	1.20
		Costs (€)	44,105.50	70,052.48	-25,946.98
2L SC MTX use - HAQ → QoL map: Drummond 2005					

NMB (€)	ICUR (€/QALY gained)	Outcome	Intervention	Comparator	Increment
87,485	-21,019	LY	26.90	26.36	0.54
		QALY	8.41	7.18	1.23
		Costs (€)	43,959.75	69,852.03	-25,892.28
2L SC MTX use - Time horizon: 5 years					
7,534	-139,580	LY	4.95	4.95	0.00
		QALY	3.05	3.01	0.04
		Costs (€)	6,265.29	11,812.00	-5,546.71
2L SC MTX use - Time horizon: 10 years					
25,727	-49,438	LY	9.74	9.74	0.01
		QALY	5.44	5.19	0.26
		Costs (€)	14,650.73	27,441.38	-12,790.65
2L SC MTX use - Time horizon: 20 years					
63,281	-27,354	LY	18.59	18.51	0.09
		QALY	8.56	7.75	0.82
		Costs (€)	30,837.47	53,214.62	-22,377.14
2L SC MTX use - Time horizon: 40 years					
85,429	-21,748	LY	26.88	26.35	0.53
		QALY	10.24	9.05	1.19
		Costs (€)	43,946.48	69,841.38	-25,894.90
2L SC MTX use - Time horizon: 80 years					
85,463	-21,732	LY	26.90	26.36	0.54
		QALY	10.24	9.05	1.19
		Costs (€)	43,959.75	69,852.03	-25,892.28
2L SC MTX use - Discount rate: 0%					
160,845	-17,608	LY	26.90	26.36	0.54
		QALY	16.62	14.24	2.38
		Costs (€)	83,720.84	125,611.81	-41,890.97
2L SC MTX use - Remove treatment in BSC (tocilizumab)					
62,821	-2,727	LY	26.90	26.36	0.54
		QALY	10.24	9.05	1.19
		Costs (€)	29,963.35	33,212.88	-3,249.53
2L SC MTX use - Concomitant MTX administration route					
84,815	-21,188	LY	26.90	26.36	0.54
		QALY	10.24	9.05	1.19
		Costs (€)	44,247.66	69,491.63	-25,243.97

ACR, American College of Rheumatology; AE, Adverse Event; BSC, Best Supportive Care; DAS; Disease Activity Score; GP, General Practitioner; HAQ, Health Assessment Questionnaire; ICUR, Incremental Cost-Utility Ratio; JAKi, Janus Kinase Inhibitor; LY, Life-Year; MTX, Methotrexate; SC, Subcutaneous; NMB, Net Monetary Benefit; QALY, Quality-Adjusted Life-Year; QoL, Quality of Life; SC, Subcutaneous; TNFi, Tumor Necrosis Factor Inhibitor.

Figure S 1 - Markov state occupancy for treatment sequence including first line subcutaneous methotrexate

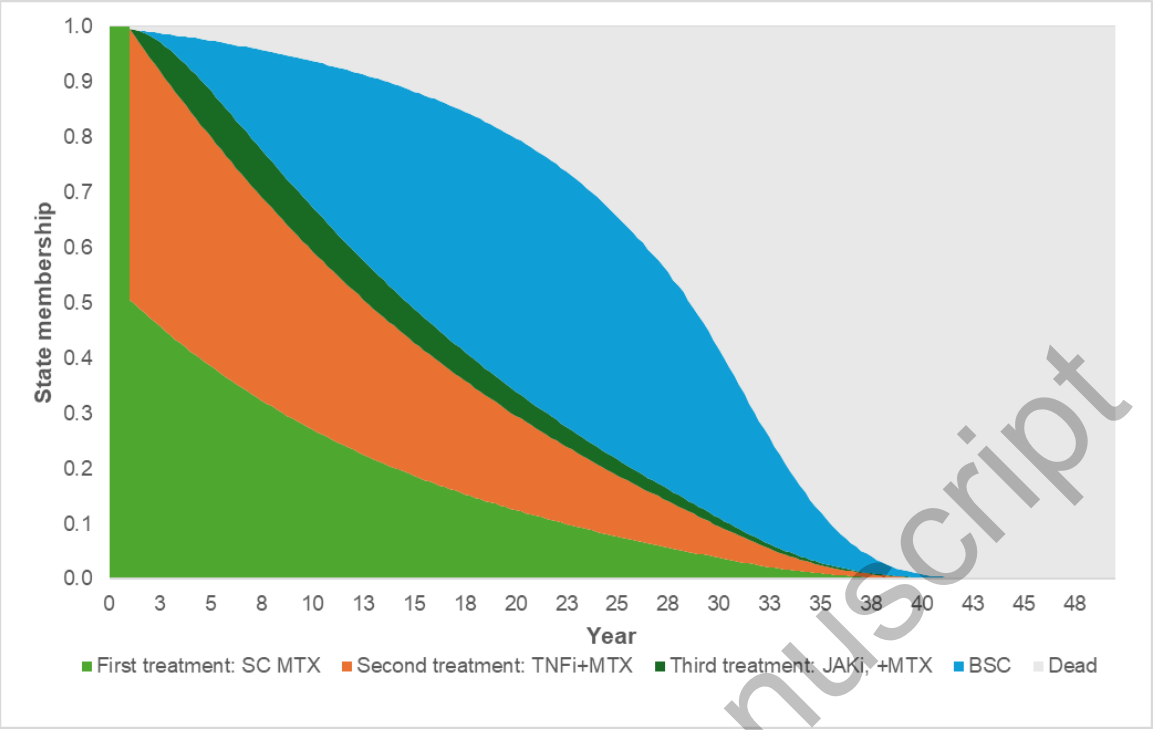
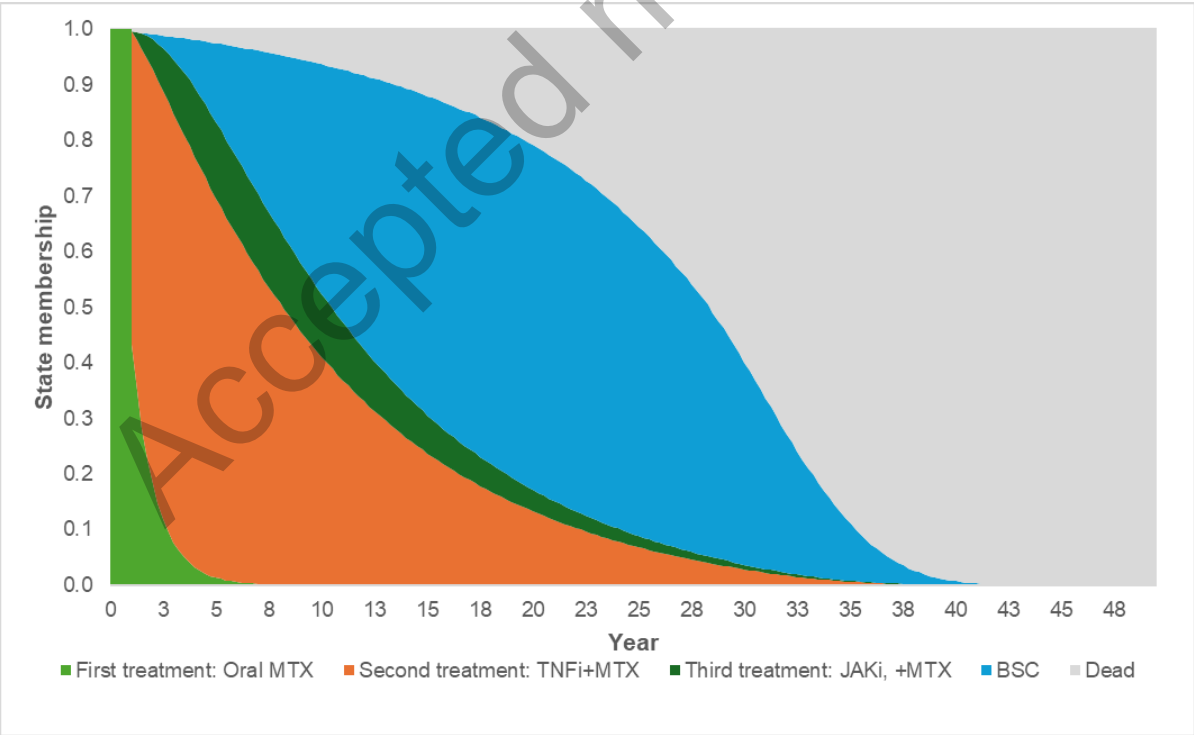


Figure S 2 - Markov state occupancy for current standard of care treatment sequence



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