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TITLE: Cost-effectiveness of TNF-blocker injections spacing for patients with established rheumatoid arthritis in remission: an economic evaluation from the Spacing of TNF-blockers injections in Rheumatoid Arthritis trial

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Highlights:

1. TNF-blocker injections spacing in RA in remission is associated with QALY loss and costs saving.
2. Treatment tapering is associated with a DCER around €50,000 saved per QALY lost.
3. Treatment tapering is debatable from an economic perspective at a societal level.

Abstract

Objective. In patients with rheumatoid arthritis in remission, a disease activity-driven tapering of adalimumab or etanercept relying on progressive injections spacing has not been shown to be equivalent to a maintenance strategy at full-dose in terms of disease activity in the STRASS trial. Nonetheless, the cost-effectiveness of such a spacing strategy remains to be evaluated.

Methods. This is a cost-utility analysis of the STRASS trial, a French multi-centre 18-month equivalence randomized open-label controlled trial which included patients at stable dose for at least 1 year, in remission for at least 6 months. Effectiveness was assessed in Quality-Adjusted Life Years (QALYs). Costs engaged within the study-period were assessed in the payer perspective. The Incremental Cost-Effectiveness Ratio (ICER) was calculated in the complete cases sample (n=98). Several sensitivity analyses were conducted and the impact of missing data on ICER estimate investigated. An acceptability analysis was performed.

Results. In the spacing-arm, TNF-blockers were stopped for 34.1% of the patients, tapered for 43.2%, maintained at full-dose for 18.2%. The spacing strategy was associated with less QALYs gain (mean difference of -0.158 [CI_{95%} -0.085 to -0.232]) and reduced costs (mean difference of €-8,440 [CI_{95%} -6,507 to -10,212]). The estimated ICER of the spacing strategy over the maintenance at full dose was €53,417 saved per QALY lost (CI_{95%} 32,230 to 104,700).

Conclusion. The spacing strategy appears cost-effective but the acceptability of such a QALY loss reported to the cost avoided remains to be evaluated, since no consensual threshold has been determined for willingness-to-accept as compared to willingness-to-pay.

Trial Registration: ClinicalTrials.gov identifier: NCT00780793. EudraCT identifier: 2007-004483-41

Introduction

Remission is the widely accepted objective for patients with rheumatoid arthritis (RA), thanks to an early and dynamic step-up therapeutic strategy based on conventional and/or biologic disease-modifying anti-rheumatic drugs (cs- or bDMARDs)[1–5]. Once this objective is achieved, treatment down-titration could be considered to lower the burden that DMARD could represent for patients, to potentially reduce DMARD adverse events – some of them being dose-dependent[6–11] – and more generally to limit patient overtreatment[12,13]. In addition, in the case of bDMARDs, step-down strategies could result in substantial cost savings for society[13,14].

Although bDMARD discontinuation has been associated with limited risk of maintaining remission or low disease activity at one year in established RA[15–18], progressive dose reduction appears more relevant from a clinical point of view. An observational study[14] assessed progressive down-titration of infliximab over 1 year and showed that down-titration was feasible in 45% of patients, with a mean dose reduction of 60%. Meanwhile, 2 randomized controlled trials showed that the risks of relapse and structural damage progression were not significantly different after 1 year of follow-up, with etanercept (ETA) either maintained at full-dose (50 mg weekly) or half-dose (25 mg weekly) [19,20].

Alternatively, a disease activity-driven tapering of bDMARD could rely on progressive injection spacing, which could represent a preferred option for patients versus reduced dosing of each injection. Two trials have investigated such an option with slightly different results. In the DRESS trial[21], injection spacing was associated with an increase in incidence of short-lived flares. However, administration of intra muscular high dose steroids and return to the previous injection interval rapidly controlled the disease and the spacing strategy was thus non-inferior to maintenance regimen in terms of persisting flares. The second study was the STRASS trial in which the spacing strategy – only based on injections spacing out or in – depending on disease activity, without rescue with high dose steroid – was considered not equivalent to the maintenance with a slight increase in disease activity and more relapses[22] (although when relapses occurred, they were successfully managed by spacing injections in). Nonetheless, in the STRASS trial, no excess risk of structural damage progression with the spacing strategy compared to full dose maintenance was evidenced. It indicates that the spacing strategy could constitute a meaningful opportunity to identify the lowest efficacious dose at a risk of relapse but no risk of irreversible damage for the patient[22]. For all these reasons, the cost-effectiveness of the spacing strategy deserves to be further investigated.

Thus, the present study is the economic evaluation based on the data of the STRASS trial, for which a cost-utility analysis comparing the two aforementioned strategies was pre-planned as a secondary analysis.

Patients and methods

Study design

The *STRASS* trial – standing for Spacing of TNF-blockers injections in Rheumatoid Arthritis Study – was a multi-centre 18-month equivalence randomized controlled trial following the PROBE (Prospective Randomized Open blinded-endpoint) methodology[23], that compared 2 therapeutic strategies in patients with established RA who achieved clinical remission with subcutaneous injection of the TNF-blocker ETA or ADA in 22 rheumatology hospital departments in France and 1 department in Monaco. The primary objective of the trial was to demonstrate the equivalence of down-titrating ETA or ADA by progressively spacing injections (S-arm), and maintaining full-regimen therapy (M-arm), in terms of disease activity[22].

Patients were randomly assigned in a 1:1 ratio to one of the 2 strategies. The randomisation list was generated by use of a computer-generated sequence with blocks of variable and undisclosed size, stratified by centre and TNF-blocker (i.e. ETA or ADA). Treatment allocation was concealed to patients, research staff and clinical staff until randomization by using an internet-based randomisation module (Cleanweb®, Telemedecine technologies S.A.S, Boulogne-Billancourt, France). Patients and clinical staff could not be further masked to treatment allocation because a sham intervention was not feasible. However, patients were unaware of study hypothesis and clinical staff unaware of aggregate outcomes during the study. Outcome assessor for the DAS 28 (primary outcome) and X-ray readers were masked to treatment allocation.

The study and all the related documents were approved for all centres by an ethics review board (CPP Ile de France VI; IRB authorization number is 100-07) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. A standardized information sheet was given to eligible patients to explain that different therapeutic strategies have been proposed for RA patients in remission without formal evaluation so far, which necessitated the conduct of trials such as *STRASS*. Written informed consent was obtained from all patients before their participation in the trial.

The present cost-utility analysis was developed according to guidelines for economic evaluations edited by the French Authority in Health[24] (HAS: “Haute Autorité de Santé”). Nonetheless, we used the payer –

health insurance (national public or private) – perspective. The time horizon was 18 months which was the follow-up period of the study.

Patients

From September 2008 to January 2011, we included patients who were ≥ 18 years old, had a diagnosis of RA according to the 1987 American College of Rheumatology (ACR) classification criteria, received subcutaneous injections of ETA or ADA at a standard and stable dosage (i.e. 50 mg weekly for ETA and 40 mg every other week for ADA) for at least 1 year as monotherapy or combined with a stable conventional DMARD (methotrexate or leflunomide) for at least 6 months. Patients receiving conventional DMARDs and prednisone (≤ 5 mg/day) concomitantly to TNF-blockers could continue these therapies at a strictly stable dose throughout the study period.

Patients needed to be in clinical remission according to the DAS28 (i.e. $\text{DAS28} \leq 2.6$) for at least 6 months with no structural damage progression seen on hand and foot X-rays in the year before inclusion according to the treating rheumatologist.

Non-inclusion criteria were of contraindications to TNF-blocker therapy maintenance, prednisone use > 5 mg/day, planned surgical intervention or pregnancy within the 18-month study period, women of childbearing age without efficacious contraception, history of cancer, diagnosis of an auto-immune disorder other than RA, non-affiliation with the French social security system, presence of factors preventing informed consent or protocol adherence (e.g., inability to communicate in the French language, mental incapacity, guardianship).

Finally, all included patients underwent clinical examination, and gave their signed informed consent to be in the trial.

Interventions

In the M-arm (maintenance), patients continued to receive TNF-blocker subcutaneous injections at the standard full regimen.

The S-arm (spacing) used a disease activity-driven approach to taper bDMARD, based on a predefined algorithm ([Figure 1](#)) that progressively spaced out subcutaneous injections according to DAS-28 score.

Figure 1. Step-down algorithm for spacing subcutaneous injections of TNF-blockers

In case of RA relapse among M-arm patients or S-arm step-0 (full dose) patients, changes in therapy were at the discretion of the rheumatologist, but patient follow-up continued to the end of the study.

Data collection

Comprehensive sociodemographic and disease characteristics as well as clinical and biological parameters were collected at the time of inclusion and every 3 months thereafter. During follow-up, visits were scheduled every 3 months for 18 months. RA clinical and biological parameters and medication were collected at each visit. Radiography of hands and feet was performed at baseline and 18 months.

Effectiveness and Cost assessment

Effectiveness was measured by means of Quality-Adjusted Life Years (QALYs). Utilities used to estimate QALYs were assessed at baseline and every 6 months using a French validated version of the EuroQoL-5D-3L (EQ-5D)[25] and French value set[26]. To adjust for baseline differences between the two-arms in health-state, adjusted QALYs were estimated by regression-based adjustment as proposed by Manca et al [27].

The global impression of the patients on their health-state was also assessed. Patients were asked at baseline and at the end of the follow-up if they found their health-state at least acceptable or not (external anchors used to assess the Patient Acceptable Symptomatic State[28] [PASS]).

For direct costs, we assessed medical consumption according to the OMERACT reference case for economic assessments[29,30]. Drugs consumption was assessed at each visit of the study every 3 months. For ETA or ADA consumption, the main bDMARDs of the study, individual costs were obtained by summing all subcutaneous injections recorded within the study-period multiplied by the price of an injection listed in the last revision of the 2014 French drug dictionary (Vidal®). For other drugs (other bDMARDs or csDMARDs, low dose of prednisone, anti-inflammatory drugs and painkillers), a standard daily price multiplied by the number of days the treatment was taken was applied. Outpatient medical doctors (MD) or health professional (HP) consultations, biologic or imaging workups, occurrence of emergency room (ER) visits, hospitalizations and inpatient care were assessed every 6 months using the Stanford Cost Assessment Questionnaire[31,32]. Individual costs were obtained by multiplying frequency of use of each item within the study period by the tariffs listed in the last 2014 revision of the national Classification of Medical Procedures (CCAM: “*Classification Commune des Actes Médicaux*”) and of the national Classification of biological tests (NABM: “*Nomenclature des Actes de Biologie Médicale*”) for MD / HP visits and imaging procedures, and for biologic

workups, respectively. Hospitalization were analysed on the basis on the International Classification of Diseases (ICD-10) main diagnosis, using the 2014 Diagnosis Related Groups (DRG) reference list. Costs were elicited on the basis of the national DRG tariff list (GHS: “*Groupes Homogènes de Séjour*”).

Productivity loss was limited to sick leave days. They were based on national average daily wages according to age, as provided by the French National Institute of Statistics and Economics Studies (INSEE: “*Institut National de la Statistique et des Études Économiques*”).

All costs were expressed into 2014 euros and were discounted at a 4% annual rate according to French HAS guidelines[24].

Statistical analyses

The maintenance strategy (M-arm) was the reference strategy. The primary cost-utility analysis was conducted using a complete-case analysis sample.: i.e. restricted to patients for which all data on costs and outcomes were available along the 18-months follow-up period.

We tested differences in costs and outcomes between the two strategies using parametric or nonparametric tests (χ^2 test, Fisher’s Exact Test for count data, McNemar χ^2 test and 2-sample Mann-Whitney Wilcoxon test) as appropriate. The difference in adjusted QALYs between the two-arms was longitudinally tested by means of a linear mixed model and post-hoc two-by-two comparisons using relevant contrasts with p-values adjusted for multiple comparisons according to the Holm-Bonferroni step-down procedure [33].

A Decremental Cost-Effectiveness Ratio (DCER) was calculated[34] by dividing the difference in costs by the difference in QALYs between the groups.

To deal with uncertainty in DCER estimation, 5,000 DCERs using 5,000 samples generated by non-parametric bootstrap were computed in order to plot a cost-effectiveness plane and to estimate a Confidence Interval at a 95% level ($CI_{95\%}$)[34].

Sensitivity analyses were performed on the assessment of QALYs. Thus, QALYs were also estimated using utilities derived from the French validated version of the SF-6D[35,36]. As a French value set is not available yet for the SF-6D, the UK value set was used [37]. Thus, QALYs were also estimated with utilities from the EQ-5D with UK value set [38], to allow comparability of the results.

Sensitivity analyses were performed on costs by decreasing the cost of each subcutaneous injection of ETA or ADA down to 70% of the current cost (to account for a plausible decrease of ETA or ADA prices in the near future in France).

The impact of missing data[39] on the results was investigated for costs and outcomes. An imputed DCER was estimated by means of Multiple Imputations by Chained Equations[40,41] (MICE) (30 datasets generated[42]).

To help decide which strategy should be promoted, two indicators were used. First, the probability of each strategy to be cost-effective for different Willingness To Accept (WTA) thresholds was computed[34]. Second, the incremental Net Monetary Benefit (iNMB) per patient for the spacing strategy (S-arm) was estimated for different WTA thresholds in euros per QALY, by multiplying the WTA threshold with the difference in QALYs and then subtracting the difference in costs. This provides an estimate of the net amount of money saved, when the possible loss of QALY is corrected for, using different WTA thresholds per QALY[34].

All statistical hypothesis tests were performed with a 5% Type I Error. All analyses were performed using R 3.1.2[43].

Results

The whole trial sample was 64 patients in the S-arm and 73 in the M-arm. Data on costs and QALYs were complete for all the 18-months follow-up period for 98 patients (71.5% of the whole trial sample sample): 44 patients (68.7% of 64) in the S-arm and 54 patients (74.0% of 73) in the M-arm (Fig 2). In the complete cases sample, 48 patients received ADA and 50 ETA with 77 in combination with a csDMARD and 21 as monotherapy. The main baseline characteristics of patients are in [Table 1](#).

Figure 2. Flow-chart of the patients enrolled in the STRASS trial cost-utility analysis

Spacing feasibility and acceptability

In the S-arm, at the 15-18 months period of follow-up, 8 patients (18.2% of 44) were receiving TNF-blocker injections at full-dose (step 0). In all, 34 (77.2%) had spaced TNF-blocker injections: 12 (27.3%) were receiving spaced-injections corresponding to step 3, 5 (11.4%) to step 2 and 2 (4.5%) to step 1; 15 (34.1%) had completely discontinued TNF-blocker treatment (step 4). In the S-arm, bDMARD treatment remained unchanged except for 2 (4.5%) patients who discontinued it due to loss of efficacy.

Between baseline and the end of follow-up, the proportion of patients which found their health state at least acceptable dropped from 95.3% to 83.7% in the S-arm (-11.6%, $p = 0.06$), while it dropped from 100.0% to 90.6% in the M-arm (-9.4%, $p = 0.02$). This difference of evolution between the two therapeutic strategies was not found to be statistically significant ($p = 0.42$).

Effectiveness and costs

At 18 months of follow-up, mean QALYs in the S-arm were 1.106 ± 0.211 (median 1.196, InterQuartile Range [IQR] 1.099-1.220) while in the M-arm it were 1.264 ± 0.146 (median 1.291, IQR 1.193-1.412) ([Table 2](#) and [Figure 3](#)). At 18 months, the mean difference between the two therapeutic strategies was -0.158 QALYs ($CI_{95\%}$ -0.086 to -0.232) ($p < 0.001$) ([Table 2](#) and [Figure 3](#)). This mean difference in QALYs was also found to be statistically significant at 12 months of follow-up ($p = 0.001$) but was not evidenced as significant at 6 months ($p=0.15$). At 18 months, this mean difference would be estimated to -0.057 ($p < 0.001$) and -0.153 ($p < 0.001$) when using utilities derived from the SF-6D or the EQ-5D both with UK value set ([Table 3](#)).

Figure 3. QALYs gain within the study-period, in each arm

At 18 months of follow-up, mean total costs were $\text{€}12,452 \pm 6,175$ (median 10,930, IQR 7,897-14,788) in the S-arm and $\text{€}20,892 \pm 1,388$ (median 20,612, IQR 20,301-21,096) in the M-arm. The cost of the treatment by ETA or ADA represented 81.0% and 92.8% of the total cost in the S and M-arm respectively. The mean cost difference between the two arms was $\text{€}-8,440$ ($CI_{95\%}$ -6,507 to -10,212) in favor of the S-arm ([Table 2](#)). The health resource use breakdown is detailed in [eTable 1](#) (supplementary material), with the related costs detailed in [eTable 2](#) (supplementary material).

DCER, acceptability analysis and sensitivity analyses

The DCER of the spacing over the maintenance strategy was estimated to be 53,417 euros saved per QALY lost (CI_{95%} 32,230 to 104,700) (Table 2). This DCER would be estimated to 55,163 and 148,070 €/QALY when using utilities derived from the EQ-5D or the SF-6D both with UK value set (Table 3).

The 5,000 bootstrapped replications (Figure 4a) showed that in all the 5,000 replications, the spacing strategy resulted in QALY loss along with cost savings. The probability of the spacing strategy to be cost-effective was 0.99 and 0.61 for WTA compensation for QALY loss thresholds at €30,000 and €50,000 respectively (Figure 4b). That is to say, if a decision-maker is willing to accept a loss in QALYs to free resources for other allocations, there is a 99% or 61% chance he/she chooses the spacing strategy if what is wanted is €30,000 or €50,000 respectively in compensation for the loss of a QALY. The iNMB of the spacing strategy is shown in Figure 4c. For WTA thresholds at €30,000 and €50,000, the mean iNMB was estimated at €3738 (CI_{95%} 477 to 6,779) and €589 (CI_{95%} -3,972 to 4,894) respectively

Figure 4. Cost-effectiveness plane and Cost-effectiveness acceptability curve

Sensitivity analyses with higher or lower ADA or ETA drug prices showed an increase or decrease of the DCER respectively. With 30% higher drug prices, the DCER would be 71,076 €/QALY (utilities derived from the EQ-5D with French value set) or 197,017 €/QALY (utilities derived from the SF-6D with UK value set). With 30% lower drug prices, the DCER would be 35,759 €/QALY (Table 3).

Missingness on costs and/or QALYs was found to be associated neither with the intervention, nor with the evolution of DAS28 during follow-up. Missingness was also not found to be associated with most of the baseline characteristics (eTable 3, supplementary material). Thus, the missing data mechanism was not assumed to be Missing Not At Random, but rather Conditionally Dependent Missing Completely at Random or Missing at Random at worst[39,44]. After MICE imputations, the DCER would be estimated to 46,261 €/QALY (mean difference in costs of -€-8,327 and mean difference of -0.180 QALYs).

Discussion

In this study, spacing TNF-blocker injections among patients with established RA in remission was found to be less effective than a maintenance strategy at full-dose (QALY loss) after 18 months of follow-up.

Nonetheless, if a decrease in the proportion of patients who found their health state acceptable was observed during follow-up, it was observed in both arms in a magnitude which was not evidenced as different between the two arms, with most patients finding their health state acceptable at the end of follow-up. Moreover, the spacing strategy was associated with a substantial cost reduction. Therefore, the DCER of the spacing strategy was estimated to be €53,417 saved per QALY lost. In addition, the spacing strategy was found to be the strategy with the highest probability of being cost-effective for WTA compensation for QALY loss threshold at €50,000.

Thus, the present study addresses one of the most difficult questions relative to cost-effectiveness assessment: is it acceptable to lower the economic burden of an innovative therapy if it is associated with a QALY loss, even though this loss is not substantial for patients and more importantly reversible? Such a question is key and hardly avoidable in the present economic context in which the funding of therapeutic innovation is a challenge for all health care payers over the world. Recently, a paper showed that the increase of insurance premiums or worker contributions was approximately 6 fold higher than inflation rate in the USA over the 2000 decade, quasi exclusively explained by the dramatic increase in drug costs[45].

Up to now, health economics assessments have often focused on incremental cost-effectiveness ratio, i.e. to determine to what extent a given health care system or society could accept to fund a new compound relative to the additional expected health gain enabled by its reimbursement[34]. However, it appears nowadays the health market growth could not continue indefinitely in a very constrained economic environment, which refers to the concept of “*degrowth*” developed by certain philosophers[46]. In the traditional health economic plan, it corresponds to a move from the north-east quadrant to the south-west quadrant ([Figure 3a](#)), i.e. from an incremental cost-effectiveness to a decremental cost-effectiveness ratio. In the first case, it corresponds to a willingness-to-pay question (“what would we willing to pay to get more health gain?”) for which more or less consensual thresholds have been proposed[32,47]. The latter case deals with a willingness-to-accept question (“What would we willing to accept as a money compensation to lose some health?”) for which only a few studies have been performed due to the innate reluctance of people to lose[48]. Thus, results from cost-effectiveness evaluation that lie in the south-west quadrant often challenge researchers and policy-makers in terms of decision-making. Indeed, they are difficult to translate easily in a language that helps interpretability. Moreover, no consensual DCER threshold have been proposed. Some could argue DCER and Incremental Cost-Effectiveness Ratio (ICER) thresholds should be identical if the goal is maximizing societal health [49]. If we apply this reasoning in this study, then a decision-maker that is willing to accept QALYs loss to free resources should

accept the spacing strategy if what is wanted is to free €30,000 to €50,000 for the loss of a QALY. Nonetheless, we acknowledge there are still differing views on the symmetry, or not, of DCER and ICER thresholds [50]. In addition, those difficulties are even more emphasized in France, where no consensual thresholds for ICER are currently used by French health authorities. Nonetheless, despite those difficulties, reporting such results are of paramount importance to reduce publication bias and to inform decision makers about all possible outcomes. The present study has some limitations. In the STRASS trial, the DCER has been estimated to be €53,417 / QALY. In another trial, the DRESS study[21], the first results of an economic evaluation identified a much higher DCER: around €390,000 saved per QALY lost[51]. This striking difference could be related, in part, to the fact that in the DRESS study as opposed to the STRASS trial, patients received high dose steroids in case of relapse, which can have dramatically reduced QALY loss.

Another limitation was the strong impact of the QALY assessment method on DCER estimates. In this study, using UK population norms, the estimated DCER was largely higher when using the SF-6D instead of the EQ-5D-3L. The low correspondence of utilities estimations when using different Multi-Attribute Utility Instruments (MAUIs) is well known[52], with still no consensus on the most appropriate MAUIs to choose[53]. In a recent study, it was estimated that this low correspondence can be partly attributed to differences in scales of each MAUIs (the range of utilities predicted by the EQ-5D-3L is 1.59 while it is 0.797 with the SF-6D), but mostly to differences in the descriptive systems (the EQ-5D-3L assumes 5 dimensions and describe 243 health states while the SF-6D assumes 6 dimensions and describe 18,000 health states)[53]. These differences may partly explain the lower mean difference in QALYs between the two therapeutic strategies reported in this study when using the SF-6D instead of the EQ-5D-3L. Indeed, when using the SF-6D, patients may have more options to report mild to moderate deviations of their health state from perfect health and therefore may have a lesser probability to report an extreme health state.

A last limitation of the study was the proportion of missing data for costs and QALYs which can have an impact on DCER estimate. Nonetheless, as missingness was found to be associated neither with the intervention, nor with the evolution of DAS28 during follow-up or with most of the baseline characteristics, it appeared to be reasonable to investigate the impact of missing data on DCER estimate by means of MICE. The imputed DCER was estimated to be €46,261 / QALY (mean difference in costs of -8,327 € and mean difference of -0.180 QALYs), close to the estimate of the complete cases analysis. Therefore, it seems that the impact of missing data could have been only a mild reduction of the difference in QALYs between the two therapeutic strategies.

However, our work has also several strengths. First, besides DCER estimates, information about patient acceptability of health state have been collected. With the PASS assessment, it appeared clearly that, although the spacing strategy was genuinely associated with a QALY loss compared to the maintenance strategy, the majority of patients continued to consider their health state acceptable. This information is clearly important and complementary to the WTA question. In addition, the structural damage assessment also showed that spacing was not associated with an increased risk of irreversible joint damage[22], which indicates a possibility for patients to return to their previous health states over the long-term. . However, the cost-effectiveness outcome of the spacing strategy has to be confirmed in longer term studies. Indeed, on one hand, spacing injections needs to be sustainable to be beneficial in costs over the long-term; on the other hand, the current short time-horizon (combined with the sample-size) can have affected the possibility to capture rare adverse events associated with bDMARDs, which can have been detrimental for the assessment of the cost-effectiveness of the spacing strategy.

Conclusion

Treatment tapering has been shown to be relevant from a clinical point of view in RA patients having achieved sustained remission. From an economic point of view, such a strategy is associated with a DCER around 50,000 € saved per QALY lost.

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Table 1. Patient characteristics at baseline

Characteristic, measure	Complete cases sample		Whole trial sample	
	Maintenance arm n = 54	Spacing arm n = 44	Maintenance arm n = 73	Spacing arm n = 64
Age, years, mean ± SD	56.0 ± 10.6	53.6 ± 9.9	56.4 ± 12.0	54.3 ± 10.7
Female sex, n (%)	38 (70.4)	35 (79.5)	54 (74.0)	53 (82.8)
Disease duration, years, mean ± SD	11.7 ± 11.2	7.2 ± 4.5	11.0 ± 10.3	8.3 ± 5.4
IgM RF positivity, n (%)	30 (66.7)	28 (70.0)	42 (67.7)	37 (68.5)
ACPA positivity, n (%)	34 (79.1)	34 (85.0)	46 (76.7)	45 (80.4)
Erosive disease on X-rays, n (%)	48 (88.9)	37 (84.1)	64 (87.7)	57 (89.1)
Swollen joint count (28 joints) , mean ± SD	0.2 ± 0.6	0.3 ± 0.7	0.2 ± 0.5	0.2 ± 0.6
Tender joint count (28 joints) , mean ± SD	0.5 ± 1.0	1.1 ± 2.2	0.7 ± 2.7	0.9 ± 1.8
ESR, mm/1st hr, mean ± SD	11.1 ± 8.5	11.6 ± 7.7	12.5 ± 10.7	12.6 ± 8.3
CRP, mg/L, mean ± SD	3.0 ± 1.9	2.6 ± 1.6	2.9 ± 2.0	2.6 ± 1.9
DAS28, mean ± SD	1.7 ± 0.5	1.9 ± 0.6	1.7 ± 0.5	1.9 ± 0.6
DAS44, mean ± SD	0.9 ± 0.4	1.1 ± 0.5	1.0 ± 0.5	1.1 ± 0.5
EQ-5D-3L VAS, mean ± SD	81.2 ± 17.4	76.6 ± 23.0	81.0 ± 17.6	76.4 ± 21.7
<i>Previous RA treatment</i>				
- Number of previous DMARDs, mean ± SD	3.0 ± 2.0	3.0 ± 2.0	2.9 ± 1.9	2.9 ± 1.9
- Patients with previous biological DMARD, n (%)	16 (29.6)	13 (29.5)	18 (24.7)	15 (23.4)
<i>On-going treatment</i>				
- Adalimumab / Etanercept, n (%)	26 (48.1) / 28 (51.9)	20 (45.5) / 24 (54.5)	34 (46.6) / 39 (53.4)	29 (45.3) / 35 (54.7)
- Monotherapy / Combination, n (%)	13 (24.1) / 41 (75.9)	8 (18.2) / 36 (81.8)	17 (23.3) / 56 (76.7)	16 (25.0) / 48 (75.0)

Note: SD: Standard Deviation, RF: Rheumatoid Factor, ACPA: Anti-Citrullinated Peptides Antibody, ESR: Erythrocyte Sedimentation Rate, CRP: C Reactive protein, DAS: Disease Activity Score, EQ-5D-3L VAS: EuroQol-5 Dimensions-3L Visual Analogue Scale, DMARD: Disease-Modifying Anti-Rheumatic Drug

Table 2. Overall costs by therapeutic strategies, QALYs gain and Decremental Cost-Effectiveness Ratio of the spacing strategy

Type of resources	Overall costs in 2014 €		Differences Mean
	Spacing arm Median [IQR]; Mean ± SD (%*)	Maintenance arm Median [IQR]; Mean ± SD (%*)	
Drugs			
<i>Adalimumab or Etanercept</i>	9,482 [6,989-12,149]; 10,089 ± 4,329 (81.0)	19,564 [19,336-19,818]; 19,390 ± 619 (92.8)	€-9,301
<i>Other bDMARDs (rescue)</i>	0 [0-0]; 377 ± 1,750 (3.1)	0 [0-0]; 0 ± 0 (0.0)	€377
<i>Other drugs</i>	238 [124-420]; 330 ± 326 (2.6)	157 [66-509]; 295 ± 273 (1.4)	€35
including csDMARDs	82 [49-115]; 119 ± 204	65 [28-115]; 95 ± 130	€24
including low dose of prednisone	0 [0-0]; 0.4 ± 2	0 [0-0]; 0 ± 0	€0
including anti-inflammatory drugs	3 [0-89]; 65 ± 89	0 [0-8]; 43 ± 85	€22
including painkillers	35 [0-317]; 145 ± 200	0 [0-305]; 156 ± 210	€-11
Other resources			
<i>Consultations + Medical Tests</i>	708 [509-869]; 808 ± 502 (6.5)	622 [475-1 005]; 758 ± 379 (3.6)	€50
including consultations	197 [136-335]; 314 ± 408	212 [131-352]; 288 ± 251	€26
including imaging workups	144 [86-261]; 197 ± 139	139 [86-284]; 197 ± 141	€0
including biological workups	221 [221-319]; 297 ± 138	221 [221-310]; 273 ± 92	€24
including other workups	0 [0-0]; 0.4 ± 2	0 [0-0]; 0.3 ± 2	€0
<i>Emergency room + hospitalization</i>	0 [0-0]; 410 ± 1,817 (3.3)	0 [0-0]; 220 ± 582 (1.1)	€190
including emergency room visits	0 [0-0]; 8 ± 29	0 [0-0]; 10 ± 31	€-2
including hospitalizations	0 [0-0]; 402 ± 1,818	0 [0-0]; 209 ± 576	€193
<i>Sick leaves</i>	0 [0-0]; 439 ± 2,118 (3.5)	0 [0-0]; 230 ± 999 (1.1)	€209
Total cost	10,930 [7,897-14,788]; 12,452 ± 6,175 (100)	20,612 [20,301-21,096]; 20,892 ± 1,388 (100)	p < 0.001
QALYs gain	1.196 [1.099-1.220], 1.106 ± 0.211	1.291 [1.192-1.412], 1.264 ± 0.146	p < 0.001
In total costs			€-8,440
In QALYs			-0.158
Cost saved per QALY lost (DCER)			53,417 €/QALY CI _{95%} : 32,230 to 104,700

Note: IQR: InterQuartile Range, SD: Standard Deviation, bDMARD: biological Disease-Modifying Anti-Rheumatic Drug, csDMARD: conventional synthetic Disease-Modifying Anti-Rheumatic Drug, QALY: Quality-Adjusted Life Year, DCER: Decremental Cost-Effectiveness Ratio, * Percentage of total costs

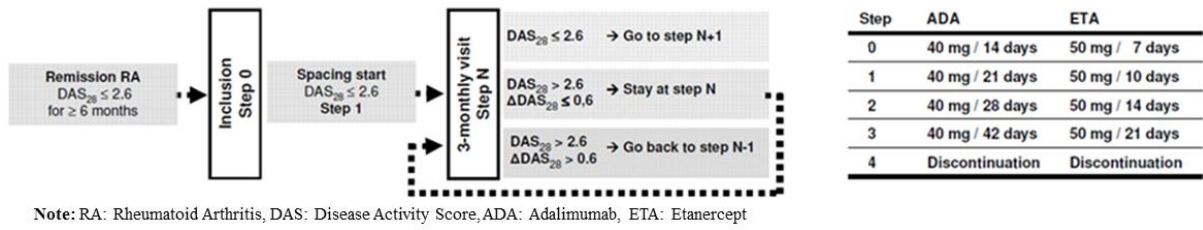
Table 3. Overall costs, effectiveness and Decremental Cost-Effectiveness Ratio estimated from sensitivity analyses

Sensitivity analysis	Mean total costs over 18 months (€)			Mean QALYs gained over 18 months			DCER (€/QALY)
	S-arm	M-arm	Difference	S-arm	M-arm	Difference	
<i>Varying the estimation of utilities</i>							
Base case, EQ-5D-3L French norms	12,452	20,892	-8,440	1.106	1.264	-0.158	53,417
SF-6D UK norms	12,452	20,892	-8,440	0.998	1.055	-0.057	148,070
EQ-5D-3L UK norms	12,452	20,892	-8,440	1.079	1.232	-0.153	55,163
<i>Varying cost of ETA or ADA</i>							
Cost down to 90%	11,444	18,954	-7,510	1.106	1.264	-0.158	47,532
Cost down to 80%	10,436	17,015	-6,579	1.106	1.264	-0.158	41,639
Cost down to 70%	9,426	15,076	-5,650	1.106	1.264	-0.158	35,759
<i>Varying utilities and cost of ETA or ADA</i>							
SF-6D UK norms and cost down to 70%	9,426	15,076	-5,650	0.998	1.055	-0.057	99,123

Note: QALY: Quality-Adjusted Life Year, DCER: Decremental Cost-Effectiveness Ratio, EQ-5D-3L: EuroQol 5 Dimensions 3L, UK: United Kingdoms, ETA:

Etanercept, ADA: Adalimumab, SF-6D: Short Form Survey 6 Dimensions

Figure 1.



Note: RA: Rheumatoid Arthritis, DAS: Disease Activity Score, ADA: Adalimumab, ETA: Etanercept

Figure 2.

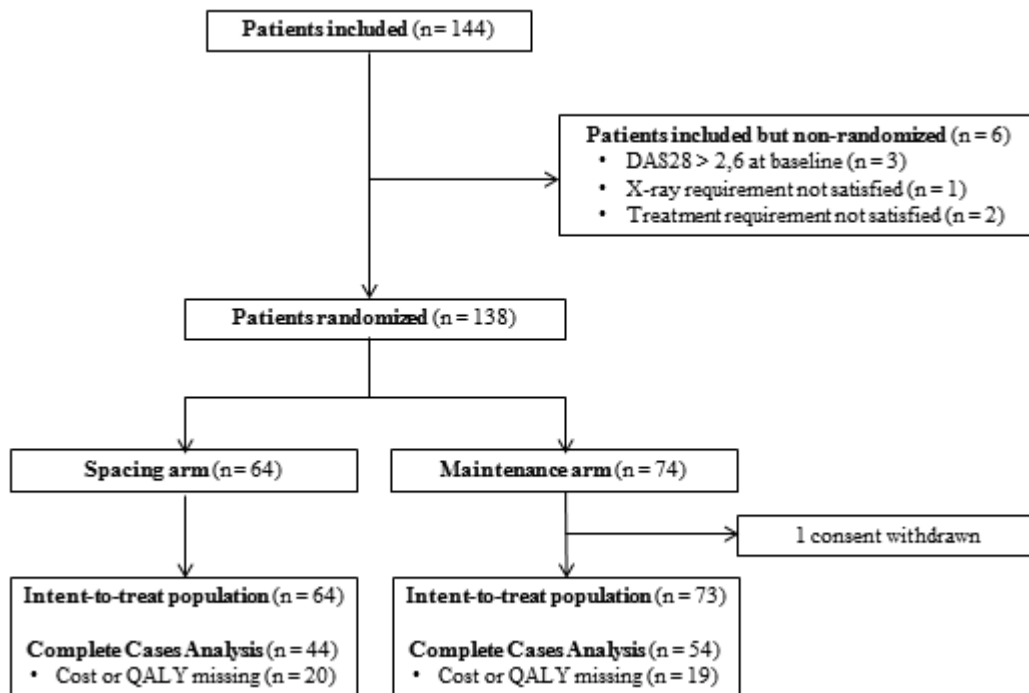
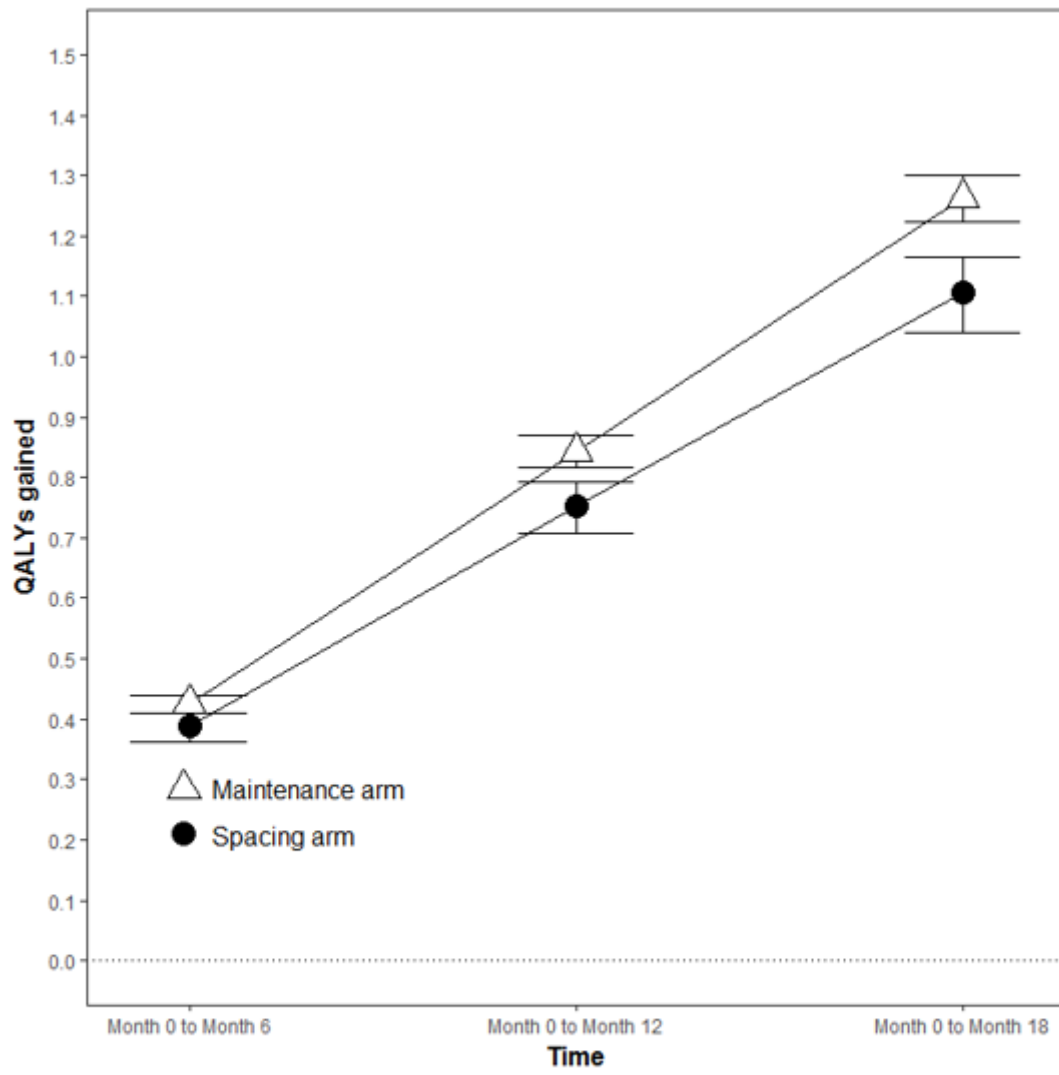
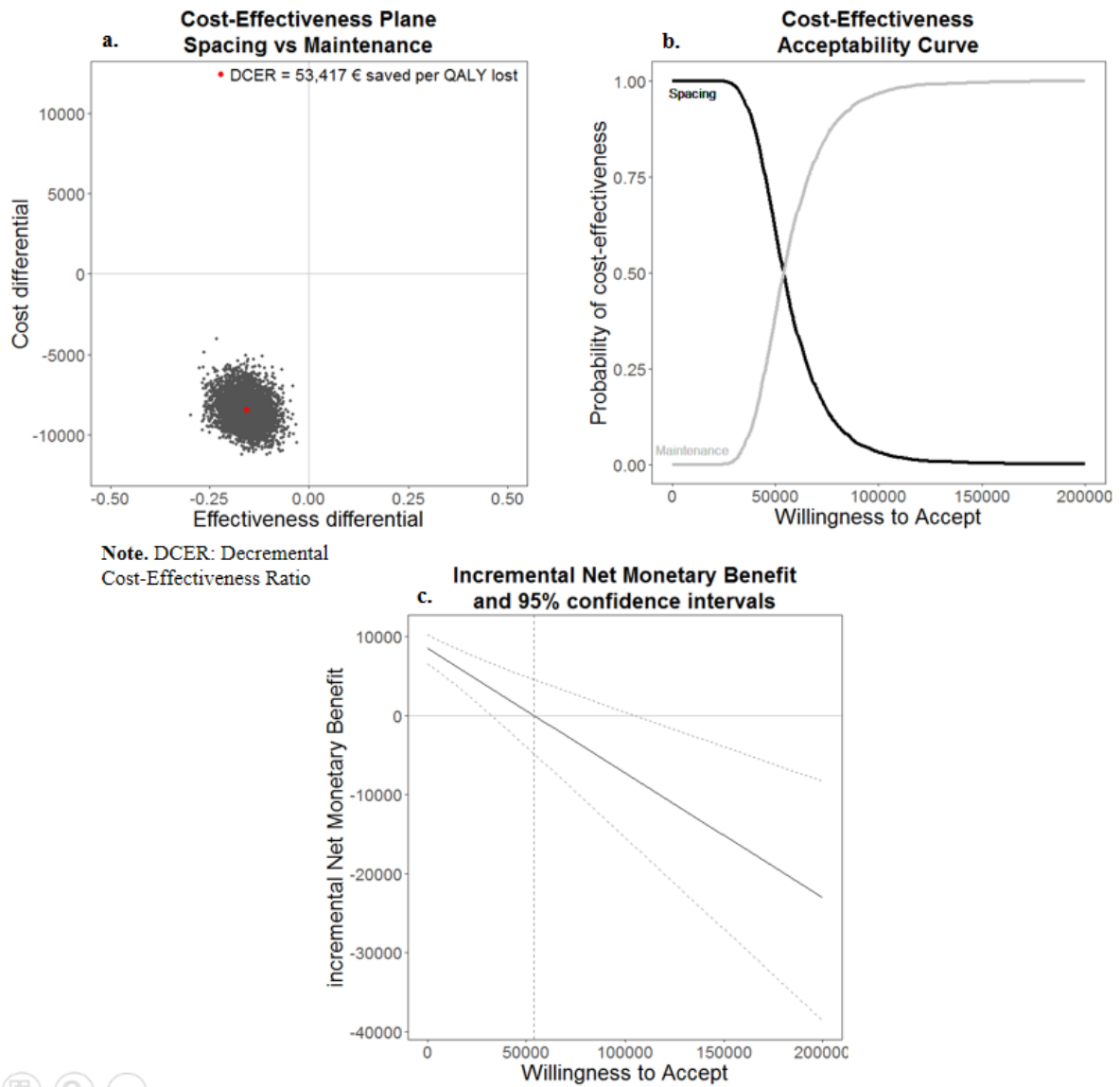


Figure 3.



Note: Points are mean values. Bar represent Confidence Interval at 95% level. QALY: Quality-Adjusted Life Year

Figure 4.



ONLINE ONLY SIUPPLEMENTS

eTable 1. Proportion of patients using resources (at least one time), by intervention, over time

Type of resources	Baseline to Month 6		Month 6 to Month 12		Month 12 to Month 18	
	M-arm N (%)	S-arm N (%)	M-arm N (%)	S-arm N (%)	M-arm N (%)	S-arm N (%)
Drugs						
Adalimumab or Etanercept	54 (100.0)	44 (100.0)	54 (100.0)	43 (97.7)	54 (100.0)	42 (95.4)
Other bDMARDs (rescue)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	2 (4.5)
csDMARDs	41 (75.9)	37 (84.1)	39 (72.2)	37 (84.1)	37 (68.5)	36 (81.2)
Low dose of prednisone	0 (0.0)	1 (2.3)	0 (0.0)	2 (4.5)	0 (0.0)	2 (4.5)
Anti-inflammatory drugs	13 (24.1)	12 (27.2)	17 (31.5)	17 (38.6)	14 (25.9)	20 (45.4)
Painkillers	21 (38.9)	17 (38.6)	23 (42.6)	20 (45.4)	20 (37.0)	17 (38.6)
Other medical resources						
Medical consultations	51 (94.4)	40 (90.9)	47 (87.0)	38 (86.4)	47 (87.0)	38 (86.4)
Imaging workups	54 (100.0)	44 (100.0)	10 (18.5)	14 (31.8)	54 (100.0)	44 (100.0)
Biological workups	54 (100.0)	44 (100.0)	54 (100.0)	44 (100.0)	54 (100.0)	44 (100.0)
Other workups	0 (0.0)	0 (0.0)	1 (1.9)	1 (2.3)	0 (0.0)	0 (0.0)
Emergency room visits	0 (0.0)	1 (2.3)	2 (3.7)	2 (4.5)	4 (7.4)	0 (0.0)
Hospitalizations	3 (5.6)	2 (4.5)	2 (3.7)	1 (2.3)	3 (5.6)	4 (9.1)
Sick leaves	1 (1.9)	3 (6.8)	3 (5.6)	2 (4.5)	4 (7.4)	3 (6.8)

Note: bDMARD: biological Disease-Modifying Anti-Rheumatic Drug, csDMARD: conventional synthetic Disease-Modifying Anti-Rheumatic Drug

eTable 2. Use of resources, in 2014 euros, by intervention, over time

Type of resources	Baseline to Month 6		Month 6 to Month 12		Month 12 to Month 18	
	M-arm Mean ± SD	S-arm Mean ± SD	M-arm Mean ± SD	S-arm Mean ± SD	M-arm Mean ± SD	S-arm Mean ± SD
Drugs						
Adalimumab or Etanercept	6519 ± 399.4	4540 ± 798.2	6553.4 ± 282.9	3126.9 ± 1992.4	6318.0 ± 187.9	2422.5 ± 2160.1
Other bDMARDs (rescue)	0 ± 0.0	0 ± 0.0	0 ± 0.0	136.3 ± 904.2	0 ± 0.0	240.3 ± 1228.4
csDMARDs	33.1 ± 43.7	40.0 ± 68.8	31.7 ± 44.1	41.2 ± 68.7	30.5 ± 42.9	37.6 ± 66.6
Low dose of prednisone	0.0 ± 0.0	0.1 ± 0.4	0.0 ± 0.0	0.2 ± 1.2	0.0 ± 0.0	0.1 ± 0.7
Anti-inflammatory drugs	14.7 ± 30.2	15.4 ± 31.2	15.2 ± 29.8	24.5 ± 34.9	13.1 ± 29.1	25.5 ± 33.5
Painkillers	52.0 ± 73.4	50.7 ± 75.7	54.6 ± 73.2	49.2 ± 64.6	49.6 ± 74.3	45.6 ± 74.3
Other medical resources						
Medical consultations	110.1 ± 121.1	88.9 ± 89.7	85.4 ± 96.3	129.2 ± 224.1	92.6 ± 96.8	95.7 ± 139.4
Imaging workups	78.7 ± 57.5	84.6 ± 69.6	26.6 ± 67.5	44.9 ± 95.7	91.7 ± 112.7	67.4 ± 58.5
Biological workups	102.1 ± 41.7	108.6 ± 59.6	70.8 ± 37.2	86.9 ± 61.5	100.1 ± 51.8	101.3 ± 50.5
Other workups	0.0 ± 0.0	0.0 ± 0.0	0.3 ± 2.1	0.4 ± 2.3	0 ± 0	0 ± 0
Emergency room visits	0.0 ± 0.0	1.8 ± 12	3.0 ± 15.2	5.9 ± 27.3	7.5 ± 27.5	0.0 ± 0.0
Hospitalizations	105.8 ± 467.5	55.8 ± 259.0	19.8 ± 102.0	222.8 ± 1477.6	83.7 ± 359.0	123.9 ± 455.5
Sick leaves	64.8 ± 476.3	56.1 ± 330.5	9.1 ± 40.0	62.4 ± 396.2	155.6 ± 890.9	320.2 ± 2008.4
Total costs	7080.5 ± 700.6	5042.0 ± 1055.0	6870.0 ± 348.5	3930.6 ± 2419.0	6942.4 ± 1028.4	3479.9 ± 3596.0

Note: bDMARD: biological Disease-Modifying Anti-Rheumatic Drug, csDMARD: conventional synthetic Disease-Modifying Anti-Rheumatic Drug

eTable 3. Association between missingness, intervention, baseline characteristics, and evolution of DAS28 during follow-up

Characteristic, measure	Complete data group n = 98	Missing data group n = 39	p
Maintenance / Spacing, n(%)	54 (55.1) / 44 (44.9)	19 (48.7) / 20 (51.3)	0.50
Age, years, mean ± SD	54.9 ± 10.3	57.0 ± 13.9	0.14
Female sex, n (%)	73 (74.5)	34 (87.2)	0.11
Disease duration, years, mean ± SD	9.4 ± 8.6	9.7 ± 6.1	0.44
IgM RF positivity, n (%)	58 (68.2)	21 (67.7)	0.96
ACPA positivity, n (%)	68 (81.9)	23 (69.7)	0.15
Erosive disease on X-rays, n (%)	85 (86.7)	36 (92.3)	0.36
Swollen joint count (28 joints) , mean ± SD	0.2 ± 0.6	0.1 ± 0.3	0.26
Tender joint count (28 joints) , mean ± SD	0.7 ± 1.7	0.9 ± 3.6	0.56
ESR, mm/1st hr, mean ± SD	11.3 ± 8.1	15.6 ± 12.3	0.05
CRP, mg/L, mean ± SD	2.8 ± 1.8	2.5 ± 2.3	0.18
DAS28, mean ± SD	1.8 ± 0.6	1.9 ± 0.5	0.18
DAS44, mean ± SD	1.0 ± 0.5	1.1 ± 0.5	0.39
EQ-5D VAS, mean ± SD	79.1 ± 20.1	78.1 ± 18.3	0.67
<i>Previous RA treatment</i>			
Number of previous DMARDs, mean ± SD	3.0 ± 2.0	2.6 ± 1.5	0.57
Patients with previous biological DMARD, n (%)	29 (29.6)	4 (10.3)	0.02
<i>On-going treatment</i>			
- Adalimumab / Etanercept, n (%)	46 (46.9) / 52 (53.1)	17 (43.6) / 22 (56.4)	0.72
- Monotherapy / Combination, n (%)	21 (21.4) / 77 (78.6)	12 (30.8) / 27 (69.2)	0.25
<i>Evolution of disease activity</i>			
Difference in DAS28 Month 0 – Month 18	-0.60 ± 1.1	-0.71 ± 1.2	0.69

Note: RF: Rheumatoid Factor, ACPA: Anti-Citrullinated Peptides Antibody, ESR: Erythrocyte Sedimentation Rate, CRP: C Reactive protein, DAS: Disease Activity Score, EQ-5D-3L VAS: EuroQol-5 Dimensions-3L Visual Analogue Scale, DMARD: Disease-Modifying Anti-Rheumatic Drug