# Preface

This article was written by Maria Kristensen at fourth semester of Medical Market Access in Medicine with Industrial Specialization at Department of Health Science and Technology, Aalborg University.

I thank the Departments of Rheumatology at Hjørring, Viborg, Horsens, Silkeborg, Fredericia, Holbæk, Gentofte and Rønne hospital for their crucial contribution to the study. Also I want to thank Annette de Thurah and Kristian Stengaard-Pedersen at Aarhus University Hospital for providing the CQR questionnaire. Louise Linde, MD and PhD, from the Department of Rheumatology at Gentofte Hospital have been very helpful during the making of this article by sharing her knowledge in rheumatology etc, and for that I want to thank her.

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The attached CD contains the questionnaire and syntax.

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# Abstract

*Objective.* To determined compliance and health related quality of life in rheumatoid arthritis (RA) patients treated with subcutaneous biologic drugs.

*Methods.* This study was designed as a cross sectional study, where RA patients completed a questionnaire containing Compliance Questionnaire Rheumatology (CQR) and EuroQol (EQ-5D). All patients enrolled had been diagnosed with RA, defined by the American College of Rheumatology (ACR) 1987 criteria, and treated with a subcutaneous biologic treatment. The study was conducted in cooperation with eight different Danish outpatient clinics. Descriptive analysis and two multiple linear models was estimated with CQR and EQ-5D as outcome.

*Results.*128 RA patients completed the questionnaire where 70.1 percent were women and the mean age were 56. The distribution of subcutaneous biologic drugs showed that most RA patients are in treatment with adalimumab and etanercept, respectively 46.8 and 43.7 percent. The mean EQ-5D score were 0,729 (range 0.223 to 1.000). The mean CQR score were 20.8 (range 1.8 to 63.2). A weak significant correlation between the administration intervals and CQR was detected. The multiple linear regression model for CQR showed increased age was associated with a worse CQR score. Similar regression model for EQ-5D indicated that female patients had worse scores, while higher education level was associated with a better EQ-5D score.

*Conclusion.* It can be concluded that the sample had a uniform EQ-5D score in relation to other studies, but scored worse on the EQ-5D score compared to the Danish population. A low CQR score was detected in proportion to RA patients treated with methotrexate indicating compliance problems among the sample. It can also be concluded that no significant correlation were found between the administrations intervals among the biologic subcutaneous drugs and EQ-5D, but a weak significant association were found between the CQR and the administration intervals. Possible explanatory factors for the CQR were found to be age, and for the EQ-5D female sex and education respectively. However it is also possible that other factors not included in this study could have an influence.

# Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory joint disease causing both pain, joint stiffness, joint deformity and subsequent lost of joint function.[1, 2] In RA, the inflammation of often multiple joints are caused by the immune system targeting the synovial membrane of the joint, thus leading to irreversible and progressive damage of the joint, cartilage and bone.[3]

Today RA is the most common form of inflammatory arthritis, and also the most serious form.[1] It can occur at any age, though the prevalence increases with age and mainly persons over the age of 45 are affected by the disease. Both incidence and prevalence data shows that women are more commonly affected then male with a relative risk of 2:3.[1, 3] However, RA tends to be more severe in men compared to women.[3] Approximately 0.7 percent of the Danish population are affected and 1.600 new patients are diagnosed every year. By the end of 2010, the nationwide registry of biological therapies in Denmark, DANBIO, had registered 3.834 RA patients who received biologic treatment, which was an increase of 500 patients per year since 2006.[4] In Denmark, the estimated cost for the biologic treatment was in 2006 503 million DKR and that increased additional in 2010 to 1.075 million DKR. The cost will expectedly increase further within the next few years. It is of course important to mention that a number of conditions are treated with biologic treatment, e.g. psoriasis arthritis, colitis ulcerosa and Morbus Crohn, but the majority of the abovementioned biologic treatments were RA patients.[5]

Overall, RA is associated with a decrease in quality of life, substantial disability and loss of work capacity. It is known that within two years after disease onset, approximately 20 percent of all RA patients are not working, as a result of their disease, and after ten years this percentage is increased to 50.[6] RA patients also have a higher risk of premature mortality, and it has been shown that life expectancy decreases with three to ten years, compared to an age-matched background population.[3, 6]

At the moment there is no cure accessible for RA patients with the current drug therapies, and symptoms associated with RA are e.g. pain, stiffness of joints, fatigue and malaise.[7] These symptoms will accelerate, if the disease is not treated, therefore it is crucial that the patients are diagnosed early and effectively treated.[2, 8] The therapy recommended for treating RA is disease-modifying antirheumatic drugs (DMARDs), and the most commonly used DMARD is methotrexate. DMARDs can inhibit the disease progression and reduce the risk of joint damage, but they have a slow acting curve in the initiate state of the treatment, which can range from several weeks to months.[2, 6, 9] The effect of DMARDs occurs within three to six months, but if not, then the treatment should be re-evaluated. A change in the treatment depends on the patient's prognosis. If the patient reports e.g. a raise in the disease activity (more than 20 joints are affected), early joint damage or if they do not respond to or tolerate the DMARDs, then the treatment should include a biologic drug.[1, 9] Over

the past decades, there has been a development of biologic DMARDs, also known as biologic drugs, as an alternative treatment to the conventional DMARD.[7, 10, 11] Nine different biologics have been approved for treatment of RA. The route of administration can be divided into intravenous infusion or subcutaneous injection and out of the nine biologics five are administrated subcutaneous, with intervals ranging from daily, weekly, every two weeks and monthly (Table 1).[7] The Danish guidelines for the first line of subcutaneous biologic treatment have been estimated and adalimumab, certolizumab pegol and etanercept was chosen in light of their effect and patient security.[4, 12]

| | **Anakinra** | **Etanercept** | **Adalimumab** | **Certolizumab Pegol** | **Golimumab** |
|---|---|---|---|---|---|
| **Brand name** | Kineret | Enbrel | Humira | Cimzia | Simponi |
| **Mode of action** | Binds IL-1 receptor | Binds TNF | Binds TNF | Bindes TNF | Binds TNF |
| **Dosage** | 100 mg once a day | 50 mg once a week | 40 mg every two weeks | 200 mg every two weeks | 50 mg once a month |

**Table 1. All subcutaneous biologic drugs approved in treatment of RA described by their brand name, mode of action and dosage.[7]**

The biologics drugs are engineered to target specific inflammatory cells, cytokines and cellular interaction which are the result of RA-related tissue damage and the RA patients will often experience an improvement in their disease state within a few weeks of treatment. The biologic drugs can reduce both signs and symptoms of RA, slow the disease progression, and improve physical function and quality of life.[6]

In a review from Callego-Calisteo et al from 2011, it was concluded that when used as treatment of RA, the biologic drugs did not vary in efficiency. Therefore, the choice of biologic drugs depends on e.g. their convenience profile, and thereby the different intervals between administration of the subcutaneous biologic drugs.[2] In theory the convenience profile could be influenced by compliance and quality of life, and can thereby have an impact on the therapeutic distribution in the course of treatment.

To the best of my knowledge, no articles have been published that investigates compliance and quality of life in RA patients in relation to the biologic subcutaneous drugs. It is important to clarify this matter, to ensure that RA patients get the optimal treatment with the most appropriate subcutaneous administrated biologic drugs. Also the biologic subcutaneous drugs are very costly. A mean average for a year treatment is 150.999,60 DKR, calculated from the total cost in 2010 for a maintenance dose[13]. Therefore, it is crucial that the RA patients have good compliance to their biologic subcutaneous treatments, both because it is costly and patients receive a better effect by administrating the drugs as prescribed by the rheumatologist.

For both compliance and quality of life no assumptions can be made about the association with the biologic subcutaneous drugs, due to the fact that no studies have been made in this area. Therefore it was the purpose of this study to determined compliance and health related quality of life by means of Compliance Questionnaire Rheumatology (CQR) and EuroQol (EQ-5D) in RA patients treated with subcutaneous administrated biologic drugs to clarify the abovementioned arguments.

# Method

This study was a cross-sectional study designed to investigate quality of life and compliance among Danish RA patients treated with biologic subcutaneous drugs. Also the study was approved by the Danish Data Protection Agency. All patients in the sample were informed in writing about the objectives of the study and ensured that the decision on completing the questionnaire was voluntary and would not have any effect on future treatment.

## Patients

Patients with RA were recruited consecutively from eight Danish outpatient clinics of rheumatology (Hjørring, Viborg, Horsens, Silkeborg, Fredericia, Holbæk, Gentofte and Rønne hospital). The inclusion criterion was a diagnosis of RA according to the American College of Rheumatology (ACR) 1987 criteria. All patients over the age of 18 and in a subcutaneous biologic treatment were included.

## Data collection

Data were collected by the use of a questionnaire, given to the patients at the outpatient clinic over a period of six weeks from the 5$^{th}$ of March to the 15$^{th}$ of April 2012. The social security number was obtained for all the RA patients who had completed the questionnaire (n = 128). From the eight departments of rheumatology, a list of all the RA patients in a subcutaneous biologic treatment was composed which contained the social security number and the currently biologic treatment (n = 570). Thereby an investigation of representatively could be conducted in proportion to gender, age and medication

According to the protocol, the questionnaire was completed by the patients at the outpatient clinic in relation to a doctor consultation or medication pick-ups. However, not all RA patients visited the outpatient clinic during the six weeks recruitment period so a part of the patients did not have the opportunity to complete the questionnaire. To calculate how many RA patients were at the outpatient clinic, but did not respond to the questionnaire during the six weeks, it can be assumed that the RA patients collect their medication approximately every three months, and these can be shared among every month (232 patients every month). In light of this, roughly 348 RA patients (232 + (232/2)) had visited the outpatient clinic in the six weeks, where 128 patients completed the questionnaire.

For clarification, the term “sample” was used in this study for describing all RA patients who had completed the questionnaire. The term “population” was used for the RA patients who had not completed the questionnaire.

The questionnaire included: age, gender, marital status, education level, occupation status and current and prior RA medication and disease onset. The presence of comorbid conditions was also uncovered from a list of 13 chronic diseases, which were found by a literature search.[14-16]

## Health related quality of life

The EQ-5D-5L was used to measure health related quality of life. The EQ-5D is a generic preference-based health status instrument and includes five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), which is divided into five levels of severity. It is not possible to estimate the health status from the EQ-5D-5L, since it is not developed yet. So a crosswalk from the value set of the EQ-5D-3L has been made to estimate the health status among the patients. The 3125 possible health status in EQ-5D-5L produced an index score ranging from 0 (death) to 1 (perfect health). The EQ-VAS was used to record the self-rated health on a 20 cm vertical, visual analogue scale, where endpoints were labelled "the best health you can imagine" at 100 and "the worst health you can imagine" at 0.[17-19]

## Compliance

The Compliance Questionnaire Rheumatology (CQR) was used in this study to examine patient compliance, which is defined as adherence to a treatment prescribed to the patients.[20, 21] To measure compliance, the CQR were used. The CQR is a 19-item compliance instrument where the patients responded to a 4-point Likert scale. Each item provides a score from one to four, which indicate how much the patients agree with the statement. The total CQR score was calculated according to GQR guidelines. The score is a continuous variable ranging from 100 (perfect compliance) to 0 (complete non-compliance).[21, 22]

## Statistical analysis

In this study Statistical Package for the Social Sciences SPSS Statistics version 18.0 was used to conduct the statistical analyses. Due to a small sample size in this study, the p-values for both 5 percent and 10 percent were considered statistically significant. A p-value of 5 percent were considered as strong, while a p-value of 10 percent were considered as week.[23]

The descriptive analysis was examined by univariable and bivariable analysis (Pearson's Chi-Squared test and two-sample t test) on age, gender and medication as outcome to test for representativity. Also descriptive univariable analysis was made for EQ-5D and CQR. A bivariable analysis was made on the basis of EQ-5D and CQR to investigate the proportions between them compared to the current biologic subcutaneous medication. For this purpose, some variables were transformed. The EQ-5D and CQR were divided into four categories to get a better illustration of the interaction. The four categories of EQ-5D were as follow; 1: 1.000-0.751, 2:0.750-0.501, 3: 0.500-0.251 and 4:0.250-0.000. The four categories of CQR were similar; 1:100-76, 2:75-51, 3:50-26 and 4:25-0. This transformation of EQ-5D and CQR was only used in the bivariable analysis, and all other analysis was made with the metric version. Current biologic subcutaneous medication was also transformed into two categories; administration once a week or less and administration

very two weeks or more. The variable administration once a week or less included etanercept and anakinra, and the variable administration very two weeks or more included golimumab, adalimumab and certolizumab pegol. This consolidation was made due to the fact that about nine out of ten patients were in treatment with adalimumab or etanercept. The transformation of the current medication was used in all statistical analysis.

In addition comorbid conditions were also transformed from the list of conditions, the patients could choose from, to whether or not the patients ever had two or more conditions, excluding RA. A scientific study has shown RA patients with two or more comorbid condition had a significant poorer quality of life compared to RA patients with one or none comorbid conditions.[24]

Two multiple linear regression models were conducted on CQR and EQ-5D as outcome to find possible explanatory variables for this study. First all possible independent variables were listed and collinearity between the variables was assessed in a correlation matrix (Appendix I). The variables number of drugs (DrugN) and number of biologic subcutaneous drugs (SubBioDrugN) were excluded for collinearity against number of biologic drugs (BioDrugN). Also the variable EQ-VAS was excluded from the regression model on EQ-5D because of EQ-VAS was part of the EQ-5D questionnaire. Then, a series of univariate regressions were made between each independent variable against the dependent variable, CQR and EQ-5D respectively, and all independent variables with p-value < 0,2 were included into the regression models (Appendix II). Before entering the independent variables, all nominal variables in the regression models were coded into dummy variables (Appendix III). The variable selection was verified by simultaneous entry of all independent variables and automated backwards selection.

# Results

## Patients

The eight outpatient clinics included 128 RA patients who completed the questionnaire. Of the 570 RA patients, that did not complete the questionnaire, approximately 220 patients may have had the opportunity to complete the questionnaire, while the rest of the patients were not at the outpatient clinic during the six weeks. The response rate between the sample and population was calculated as 18.3 percent, but the response rate on basis of the sample and the non-responders could be calculated as 36.8 percent. This response rate can only be approximately calculated due to the fact that it was not possible to estimate the exact number of non-responders.

The distribution of gender among the sample and population appeared relative identical, respectively 70.1 percent and 72.6 percent women (Table 2). The two groups of gender were investigated for representativity and the proportions between the two independent groups were found to be the same ($p = 0.585$). Distribution of age in the sample showed that mean age were 56 (range 19-83) and median age were 57. The population showed similar distribution with mean age at 58 (range 19-89) and median age were 59. The representativity were also investigated in this variable, and the difference between the two independent population means were found to be comparable ($p = 0.397$). The distribution in medication was also investigated, and the majority of patients both in the sample and population were in treatment with adalimumab or etanercept. When medication of the sample and population were investigated the proportions between them were found to be significantly different ($p = 0.002$).

| Descriptive analysis | | | |
|---|---|---|---|
| **Variable** | **Sample** | **Population** | **P** |
| **Gender (mean)** | | | |
| Woman | 70.1 | 72.6 | 0.585* |
| Men | 29.9 | 27.4 | |
| **Age** | 56 (19-83) | 58 (19-89) | 0.397¤ |
| **Medication (%)** | | | |
| Certolizumab pegol | 3.2 | 7.9 | 0.002* |
| Etanercept | 43.7 | 40.2 | |
| Adalimumab | 46.8 | 40.9 | |
| Golimumab | 4.8 | 11.1 | |
| Anakinra | 1.6 | 0 | |
| **Marital Status (%)** | | | |
| Single | 31.3 | | |
| Married/cohabitant | 68.7 | | |
| **Employment (%)** | | | |
| Full-time employee or student | 28 | | |
| Out of work or part-time employee | 24.8 | | |
| Pension or incapacity benefit do to RA | 47.2 | | |
| **Education (%)** | | | |
| Attended or finishing government school | 27 | | |
| Finishing youth education programme | 18.3 | | |
| Finishing a higher education | 54.8 | | |
| **Comorbid conditions (%)** | | | |
| Yes | 21.9 | | |
| No | 78.1 | | |
| **Disease duration (mean yrs)** | 12.96 (1 - 41) | | |
| **Prior drugs (mean n)** | 4.5 (1 - 11) | | |

**Table 2. Descriptive analysis made on the variables gender, age and medication for both the sample and the population. Representativity is investigated between the sample and the population with bivariable analysis. A p-value of either 5 % or 10 % was not relevant. *Chi-squared test $X^2$. ¤Two-sample t test. Also descriptive analysis is made on the variable marital status, employment, education, comorbid conditions, disease duration and prior medication for the sample. All values are percentile (min - max) unless otherwise stated. Prior drugs includes all previous drugs treating RA.**

The majority of the sample was married or cohabitants received a pension or incapacity benefits do to RA and had finished a higher education. They also had no comorbid conditions, a disease duration of nearly 13 years and have previous been treated with 4.5 different drugs in relation to RA.

## Questionnaire analysis

To evaluate EQ-5D and CQR both descriptive analysis and multiple linear regression models were conducted. The EQ-5D and CQR scores are shown in Table 3. Of all the patients in the sample, 126 patients completed the CQR, which means only two missing values from the sample of 128. The mean value was found to be 20.8 with a range from 1.8 to 63.2, and the median was 19.

| | Mean | Median | SD | SE | Minimum | Maximum |
|---|---|---|---|---|---|---|
| EQ-5D (N = 125) | 0.729 | 0.733 | 0.146 | 0.013 | 0.223 | 1.000 |
| CQR (N = 126) | 20.8 | 19.3 | 11.2 | 1.0 | 1.8 | 63.2 |

Table 3. Descriptive statistics of EQ-5D and CQR on the variables mean, median, SD, SE, minimum and maximum.

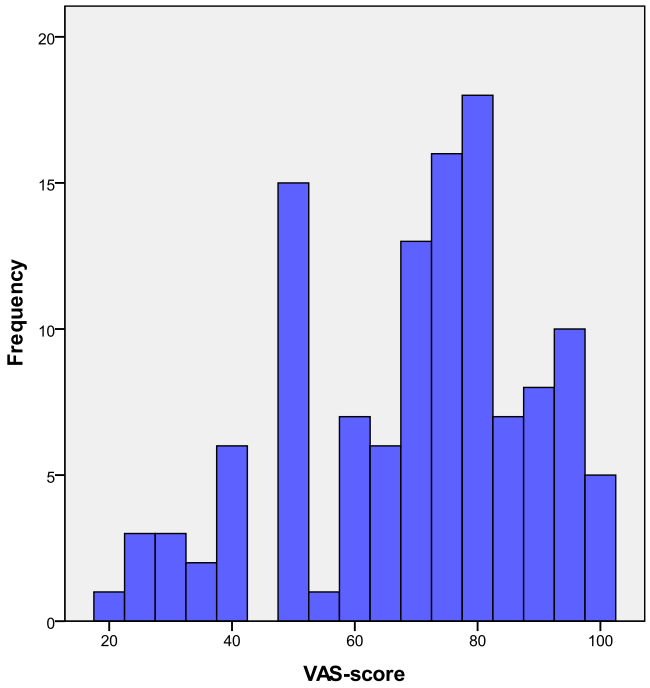


Figure 2. The distribution of VAS.

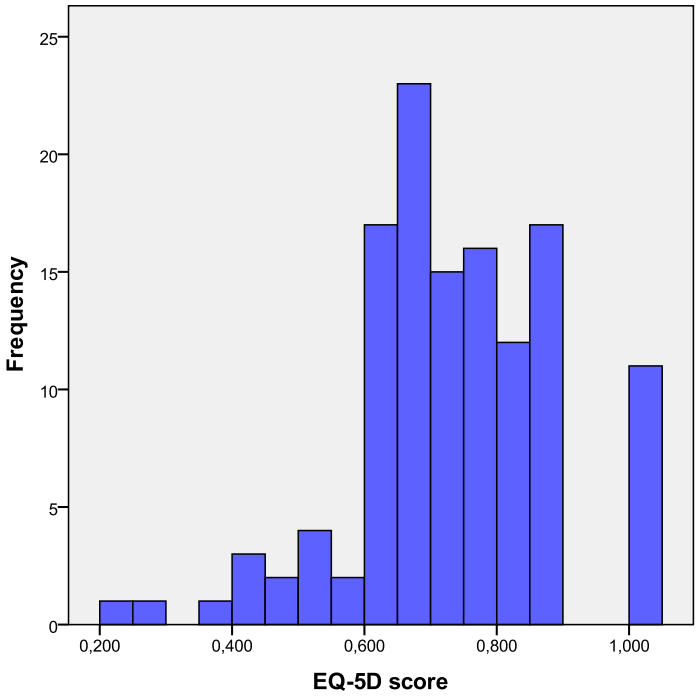


Figure 1. The distribution of EQ-5D.

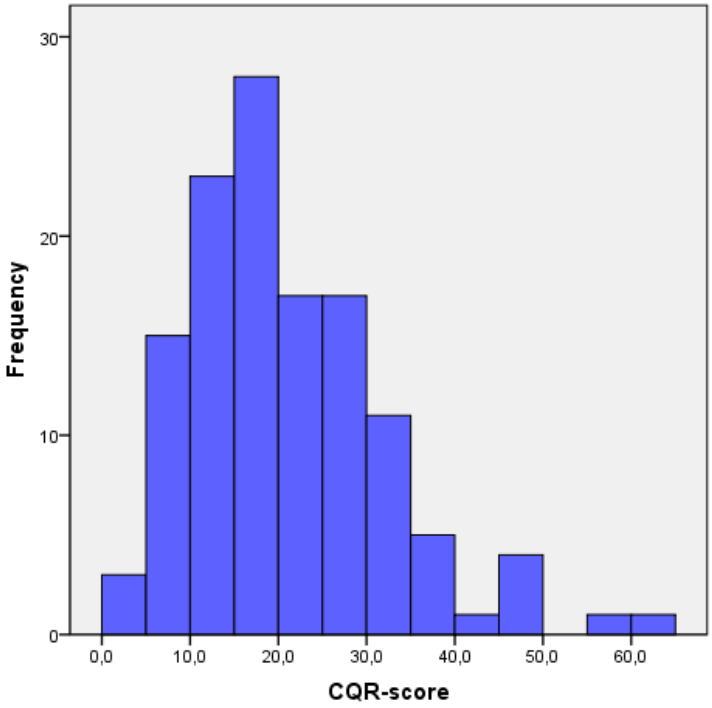


Figure 3. The distribution of CQR.

The 125 patients who completed the EQ-5D, and missing values were three. The mean value was 0.729 with a range of 0.223 to 1.000, and the median value was 0.73. In addition to the EQ-5D, the distribution of EQ-VAS was explored in Figure 2. It showed that the data were right-skewed. The distribution of EQ-5D (Figure 1) also showed that the data were right-skewed, consistent with the EQ-VAS. The distribution of CQR (Figure 3) was, contrary to EQ-5D and EQ-VAS, left-skewed.

Correlation between EQ-5D, CQR and biologic subcutaneous medication were investigated (Figure 4). No correlation between EQ-5D and both CQR and biologic subcutaneous medication were statistical significant. The correlation between biologic subcutaneous drugs and CQR were found to be weakly significant at a 10 percent level, and the correlation coefficient was -0.159 indicating a negative, but closely no, association between the two variables.

**Correlation between EQ-5D, CQR and biologic subcutaneous drug**

| Correlation | Pearson's r | Spearman's rho | p |
|---|---|---|---|
| EQ-5D – CQR | 0.038 | - | 0.674 |
| Sub.Bio – EQ-5D | - | 0.015 | 0.871 |
| Sub.Bio - CQR | - | -0.159 | 0.080* |

**Figure 4. Correlation between EQ-5D, CQR and biologic subcutaneous drugs. Biologic subcutaneous drugs refer to type of drug (administration every week or less and every two weeks or more). *significance at 10 % level.**

The distribution among the biologic subcutaneous medication in relation to the CQR score and the EQ-5D score were investigated (Appendix IV). The distribution showed that the two administrations groups seemed equal and most patients had a high quality of life (the majority of patients were in division 1 and 2) and also a low compliance (division 3 and 4). The distribution of the biologic subcutaneous medication in relation to gender and age were also investigated (Appendix IV). It showed that the two administrations groups were relatively equal among woman, while a big part of men were in treatment with drugs administrated every two weeks or more. In relation to age, the two administrations groups seemed equal among patients at 18 to 37 years, the 58 to 77 years and the 78 to 97 years. There was however a difference among the administrations groups for patients between 38 to 57 years, where a relatively big part of the patient was in treatment with drugs administrated every two weeks or more.

The final multiple linear regression model for CQR is presented in Table 4. Five out of nine independent variables were significantly associated with the CQR score due to univariate regressions (Appendix II). From the five independent variables only one variable was significant in the multiple linear regression model,

namely age. Higher age was associated with worse CQR score. No variables showed significance at 10 percent level in the regression model.

**Multiple linear regression for CQR**

| Variable | Coefficient | Estimated value | 95 % CI | p |
|---|---|---|---|---|
| Constant | $B_0$ | 34.3 | 26.574 to 41.998 | <0.001* |
| Age | $B_1$ | -0.24 | -0.376 to -0.104 | 0.001* |
| Pension and incapacity benefit do to RA | | -3.83 | -8.54 to 0.881 | 0.110 |
| Comorbid condition | | -2.06 | -7.155 to 3.04 | 0.426 |
| Out of work and part-time employee | | -2.152 | -7.492 to 3.187 | 0.426 |
| Disease duration | | -0.008 | -0.241 to 0.226 | 0.949 |

**Table 4. Final multiple linear regression model with CQR as outcome including the explanatory variables that were insignificant. The variable age indicates the exact age of the patients. *significance at 5 % level. No variables showed significance at 10 % level.**

Also the final multiple linear regression model for EQ-5D was made and presented in Table 5. Of the nine independent variables, only four were significantly associated with the EQ-5D score due to univariate regressions (Appendix II).

**Multiple linear regression for EQ-5D**

| Variable | Coefficient | Estimated value | 95 % CI | p |
|---|---|---|---|---|
| Constant | $B_0$ | 0.698 | 0.621 to 0.774 | <0.001* |
| Female sex | $B_1$ | -0.07 | -0.123 to -0.016 | 0.011* |
| Education | $B_2$ | 0.036 | 0.008 to 0.064 | 0.012* |
| Pension and incapacity benefit do to RA | | -0.044 | -0.101 to 0.014 | 0.136 |
| Out of work and part-time employee | | -0.031 | -0.088 to 0.026 | 0.290 |

**Table 5. Finale multiple linear regression model with EQ-5D as outcome including the explanatory variables that were insignificant. Reference groups: male. Education included attended or finishing government school, finishing youth education programme or finishing a higher education. *significance at 5 % level. No variables showed significance at 10 % level.**

Two out of four variables were found to be significant in the multiple linear regression, female sex and education respectively. Women had worse EQ-5D score compared to men, however an increase in education level (from attended or finishing government school to finishing youth education programme or to finishing a higher education) was associated with better EQ-5D. No variables showed significance at 10 percent level in the regression model.

# Discussion

In this study, compliance and health related quality of life was investigated by a cross-sectional design on a population of 128 RA outpatients in RA patients treated with subcutaneous biologic drugs, giving insight into the distribution of the CQR and the EQ-5D, association between the CQR, the EQ-5D and the administration intervals among the biologic subcutaneous drug and potential explanatory variables.

The strengths of the study included good data quality with very little missing data in relation to the EQ-5D (125 responder) and CQR (126 responder). The patients were recruited from eight out of 25 Danish clinics in different geographic areas and environments (from small clinics with seven patients to larger clinics with 149 patients). Though, there are differences in the Danish regional distribution of both RA patients and the use of biologic drugs as a result of varying research projects and recommendations among the regions[5]. Therefore it can be discussed whether or not the results in this study reflects the regional differences.

The limitations of the study are related to the relative small sample size. The response rate between sample and population were 18.3 percent, which is low and therefore also a limitation. Though, the response rate between the sample and the non-responders could not be precisely established, an estimate was calculated to be 36.8 percent. The estimate is relatively higher compared to 18.3 percent, but is still considered low. Do to the cross sectional design, cause and effect in relation to the multiple linear regression models could not be detected, but the outcome of the regression models could provided an illustration of possible explanatory factors, knowingly that other factors not included in this study may also have an influence.

It was found that within the two variables, age and gender, there was representativity between sample and population. This was not the case with the variable medication even though the distribution of medication within the sample seemed equal with the population, though not enough for the two groups proportions to be significant equal. There has been established a connection to DANBIO, and a register demand has been requested for the variables DAS28 (number of swollen and tender joints), HAQ (the Health Assessment Questionnaire) and disease duration, which could be included into the representativity table. The DAS28 and HAQ would illustrate how ill the patients are, and it would be tested whether or not the population suffering from a more severe state of disease then the sample, and if this could be the reason for their non-response. Respectively, it could also be tested whether or not the population are less disabled by their disease then the sample. The disease duration could contribute to the aforementioned thesis, due to the fact that long term RA patients tend to have a more severe state of disease compared to newly diagnosed patients. Though this register demand was not accessible before the deadline of this article, it should be available for the publication of the article.

The overall median score for EQ-5D was in the sample 0.733, and this was consistent with other studies of EQ-5D in RA patients.[14, 25] In a study among a random sample of the Danish population, the EQ-5D score was investigated, and it showed that the score ranged from 0.93 to 0.83.[26] This illustrates that the RA patients in the sample had lower quality of life compared to the Danish population, which could be due to the fact that the disease affects the patients by causing severe symptoms.

The overall median score for CQR was found to be 19.3. In a study investigating compliance in RA patient treated with methotrexate, which is administrated once a week, the median CQR score at baseline was found to be 70.1.[22] This illustrates that the RA patients in this study had a very low compliance compared to RA patients treated with DMARD. The reason for the low compliance score in this study could be related to the questions in the CQR, where the statements can be interpreted differently among the sample and thereby influencing their score. It could also be that the patients in the sample just are more non-compliant in regards to their treatment compared to RA patients treated with DMARD.

The distribution between the administration intervals of the biologic subcutaneous medication and the EQ-5D and CQR, respectively, have shown that patients in the sample, nine out of ten, have a relatively high EQ-5D score, ranging between 0.500 and 1.000, and low compliance, ranging from 0 to 50 divided almost equal between administration intervals. This could illustrate why the sample have a low compliance, namely because the patients have a high quality of life and feeling somewhat cured resulting in e.g. delay of the administration or missing injections.

To investigate whether or not the administration interval had any influence on the EQ-5D and the CQR, correlation analysis was made. This showed that there was no significant correlation between the administration intervals and EQ-5D in the sample, even though it had been expected that the different drug administration intervals could have an influence on the EQ-5D. A weakly significant correlation between the administration intervals and CQR was revealed, which indicated a small, but negatively correlation. This means that the larger administration intervals, the worse CQR score.

The distribution of age and gender in proportion to the administration intervals were investigated to detect possible variations among the administration intervals in relation to age and gender. Variation was found among men, where a big part of the sample was treated with drugs administrated every two weeks or more. This was also the case with patients at the age of 38 to 57. This could be a result of a clinical knowledge among the treating doctors, where male patients between the ages of 38 to 57 respond better to drugs administrated ever two weeks or more. This could also just be a coincidence.

In relation to finding explanatory factors for both CQR and EQ-5D, it was revealed that higher age were associated with worse CQR score. It makes sense that older people have some trouble managing the treatment. Though, it also illustrates that initiatives have to be made to accommodate this issue. Explanatory

factors for the EQ-5D score were found to be i.a. female sex, which is not surprising giving that woman in general often expresses worse mental and physical health[27]. Also education was an explanatory factor for the EQ-5D, where higher education results in better EQ-5D score, which also were expected giving that higher education has been shown to be associated with better mental and physical health[27]. It is important to take into consideration that other factors that were not part of this study could also have an influence. It was expected for both CQR and EQ-5D that more variables had an influence, but a possible explanation could be that the sample size was simply too small to detect further associations between variables.

The causes of high compliance versus non-compliance have been studied in many chronic diseases, though the findings are inconsistent[28, 29], therefore it can be argued whether compliance are increased with higher administration interval or reverse. Likewise, quality of life can increase with higher administration interval or reverse. In this study, new data have been revealed on this field, but various studies have to be made, perhaps a prospective cohort study with a larger sample, to determined further association between the administration interval and the CQR and the EQ-5D.

# Conclusion

In summary, this sample of RA patients in a biologic subcutaneous treatment had a consisting EQ-5D score in relation to other studies, but scored worse on the EQ-5D score compared to the Danish population. Furthermore, a low CQR score was detected compared to RA patients treated with methotrexate indicating compliance problems among the sample. It can be concluded that no significant correlation were detected between the administrations intervals among the biologic subcutaneous drugs and EQ-5D, but the association between the CQR and the administration intervals was found to be significant at a 10 percent level. It can also be concluded that possible explanatory factors for CQR were found to be age, and for EQ-5D it was female sex and education respectively, though it is most possible that other factors not included in this study can have an influence.

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# Appendix I

**Correlation matrix**

| Variable | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 Gender | | | | | | | | | | | |
| 2 Age | **-0.204** | | | | | | | | | | |
| 3 Medication | -0.107 | 0.031 | | | | | | | | | |
| 4 Employ | **0.323** | **0.708** | 0.428 | | | | | | | | |
| 5 Education | 0.092 | 0.041 | 0.165 | **0.326** | | | | | | | |
| 6 Marital Status | **0.281** | 0.622 | **-0.193** | **0.328** | 0.006 | | | | | | |
| 7 Disease Duration | -0.047 | **0.395** | **0.184** | 0.504 | 0.097 | -0.022 | | | | | |
| 8 EQ-VAS | -0.091 | -0.095 | -0.037 | 0.546 | 0.070 | 0.039 | -0.030 | | | | |
| 9 Comorbid conditions | -0.065 | 0.691 | 0.045 | **0.364** | -0.006 | **-0.194** | **-0.249** | -0.088 | | | |
| 10 DrugN | 0.087 | 0.029 | 0.133 | 0.274 | **0.228** | 0.056 | **0.495** | -0.046 | -0.044 | | |
| 11BioDrugN | -0.43 | -0.105 | 0.052 | 0.255 | 0.055 | 0.020 | 0.129 | -0.037 | -0.049 | **0.479** | |
| 12 SubBioDrugN | 0.081 | -0.058 | -0.005 | 0.235 | 0.071 | 0.113 | 0.061 | -0.124 | 0.045 | **0.360** | **0.714** |

**Correlation estimates in bold indicate a significance at 5 % level. Age: The exact age (years). Medication: The present biologic subcutaneous drug (administration every week or less and every two weeks or more). Employ: Present employment (Full-time employee and student, out of work and part-time employee or pension and incapacity benefit do to RA). Education: Attended or finishing government school, finishing youth education programme or finishing a higher education. Marital status: Married/cohabiting or single. Disease duration: Time (years) the patients have been diagnosed with RA. EQ-VAS: The exact score. Comorbid conditions: Two or more conditions including RA (yes/no). DrugN: Number of drugs the patients has been treated with for RA (including for instance NSAID, DMARD and biologic subcutaneous drugs). BioDrugN: Number of biologic drugs the patients has been treated with for RA (including DMARD and biologic subcutaneous drugs). SubBioDrugN: Number of biologic subcutaneous drugs the patients has been treated with for RA.**

# Appendix II

**Univarite regression CQR**

| Variable | p |
|---|---|
| Gender | 0.568 |
| Age | 0.001* |
| Medication | 0.269 |
| Employment | 0.003* |
| Education | 0.612 |
| Marital Status | 0.232 |
| Disease Duration | 0.172* |
| Comorbid conditions | 0.025* |
| Number of biologic drugs | 0.389 |
| EQ-VAS | 0.539 |

***p-value under 0.2 was included in the multiple linear regression model. *significance at 5 % level. No variables showed significance at 10 % level.**

**Univarite regression EQ-5D**

| Variable | p |
|---|---|
| Gender | 0.015* |
| Age | 0.619 |
| Medication | 0.590 |
| Employment | 0.104* |
| Education | 0.023* |
| Marital Status | 0.802 |
| Disease Duration | 0.235 |
| Comorbid conditions | 0.793 |
| Number of biologic drugs | 0.979 |

***p-value under 0.2 was included in the multiple linear regression model. *significance at 5 % level. No variables showed significance at 10 % level.**

# Appendix III

| | Dummy variable | |
|---|---|---|
| | $D_1$ | $D_2$ |
| **Gender:** | | |
| - Woman | 1 | |
| - Men | 0 | |
| **Employment:** | | |
| - Full-time employee and student | 0 | 0 |
| - Out of work and part-time employee | 1 | 0 |
| - Pension and incapacity benefit do to RA | 0 | 1 |
| **Comorbid conditions:** | | |
| - Yes | 1 | |
| - No | 0 | |

**Dummy variables made on the nominal variables gender, employment and comorbid conditions.**

# Appendix IV

| | | Biologic subcutaneous medication | |
|---|---|---|---|
| | | Administration once a week or less | Administration every two weeks or more |
| **CQR score** | 100-76 | 0 | 0 |
| | 75-51 | 1 | 1 |
| | 50-26 | 19 | 17 |
| | 25-0 | 35 | 49 |
| **EQ-5D score** | 1.000-0.751 | 25 | 30 |
| | 0.750-0.501 | 29 | 30 |
| | 0.500-0.251 | 0 | 5 |
| | 0.250-0.000 | 0 | 1 |

**Contingency table of the divisions of biologic subcutaneous medication in relation to EQ-5D and CQR, respectively. Both EQ-5D and CQR was made into divisions of four - EQ-5D; 1: 1.000-0.751 2:0.750-0.501 3: 0.500-0.251 4:0.250-0.000. CQR; 1: 100-76 2:75-51 3:50-26 4:25-0.**

| | | Biologic subcutaneous medication | |
|---|---|---|---|
| | | Administration once a week or less | Administration every two weeks or more |
| **Gender** | Women | 19 | 16 |
| | Men | 36 | 52 |
| **Age** | 18 – 37 | 7 | 6 |
| | 38 – 57 | 21 | 34 |
| | 58 – 77 | 25 | 25 |
| | 78 - 97 | 2 | 3 |

**Contingency table of the divisions of biologic subcutaneous medication in relation to gender and age, respectively.**