Analysis of Electronic Medical Records of Rheumatoid Arthritis Patients on Biological Therapies
A Reuma.pt Study

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Abstract

Motivation
Rheumatoid arthritis (RA) is one of the lead causes of disability in the western world and is linked with reduce life quality and decreased life expectancy. In addition, about 60% of the patients fail treatment and is known that early intervention might prevent, among other things, irreversible damage to the joints.

Objectives
Investigate Electronic medical records (EMR) from Reuma.pt and increase the base knowledge about the use of biologic drugs for RA in clinical-practice. Explore the data and find meaningful patterns in it. Estimate the chances of remission for the different biologics.

Materials & Methods
EMR from Reuma.pt register. All the 436 patients are diagnosed with RA and are or were treated with biological agents. Descriptive analysis of the data. Analysis of summary measures. Kaplan-Meier curves for remission(s). Model selection for stratified Cox proportional hazards regression for the first remission. Analysis of recurrent events.

Findings
Tocilizumab was the most efficacious therapy in most of the analysis (HR, 2.28, 95% CI, 1.00 to 5.19, P=0.0495). There was no remissions with anakinra, remission was 73% less likely with adalimumab (HR, 0.27, 95% CI, 0.10 to 0.70, P=0.007, ref: etanercept) and the ones on rituximab had 88% less chances of remission than the reference group (HR, 0.12, 95% CI, 0.03 to 0.58, P=0.008). RA duration, age, weight and patient global assessment VAS at baseline were also negatively associated with remission. The erythrocytes sedimentation rate was positively associated with remission.

Conclusions
Tocilizumab was the most efficacious therapy, anakinra had no remissions and rituximab and adalimumab were less efficacious comparing to etanercept. Further studies need to be done.

Keywords: Rheumatoid arthritis, Biological therapies, Electronic medical records, Cox regression

1 Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that causes a chronic inflammatory response of the synovial membrane with consequent cartilage destruction and bone erosion within the joint. The main clinical manifestations of the disease are joint pain, stiffness and excess synovial fluid in symmetrical joints causing swelling of the synovium mostly on the hands and feet. The disability in RA patients develops most rapidly during the first 2 years of disease when the constant insult to the synovium leads to the gradual replacement of this tissue by fibrous tissue [1]. For this reason, early identification and aggressive intervention in RA is fundamental to minimize the irreversible functional damage in the joints.

Biological therapies for RA are called this way because they are produced in other organisms by recombining human genes of antibodies against a specific target. Because of their production method the price is much higher than the synthetically produced disease modifying anti-rheumatic drugs (DMARDs).

Biological therapies are divided in two classes: the tumor necrosis factor (TNF) antagonists (or anti-TNF) and the non-TNF antagonists. Anti-TNF is usually the first class of biologics given to RA patients.

This article studies the effect of the different biological therapies and of other factors that might influence the chances of remission.

2 Materials and Methodology

2.1 Data

The object of study of this thesis is EMR extracted in June 2014 from the Reuma.pt database. The patients records come from observational data from two health centers registered in Reuma.pt. There are 9305 observations from a total of 436 patients, 78 of which had already started biological therapies before the follow-up start. All the patients are diagnosed with RA and are or were treated with biological agents.

The data consists of demographic information, pharmaceutical records, disease activity and disability
indicators, response to biological therapy and other clinical data. The data can be described as a retrospective, observational, and as unbalanced longitudinal data. The last description means that the patients have repeated measures during the follow-up period but there is not the same number of observations per patient. In addition, during the follow-up time, a patient can switch between therapies or be unenrolled on therapy. The largest follow-up time for a patient in the data was almost 15 years and the smallest was just one appointment. See Figure 1 for an real example of the structure of the data.

The information about DMARDs and GCs was collapsed to form a unique variable to each one of them. The dates of the appointments was encoded according with the season of the year to investigate possible seasonality of the disease flare or remission. Variables with a large number of levels were recategorized to ease the analysis and because some groups did not have enough observations and the methods were not converging. This happened, for example, with the variables for race, drinking habits and smoking habits.

Having in attention that most of the subjects experienced different drugs at different times, only one of the drugs per subject was selected.

By observing different estimates for disease activity, there were few subjects at risk and almost no new events after 4 years. Therefore, the follow-up time was initially limited to 4 years. From this dataset was then extracted the time to remission data used for the KM estimate and Cox regressions. This dataset was called dataset A.

2.2 Data analysis

The descriptive analysis used smoothed and kernal density estimates for the DAS28 over time by therapy.

Next, each one of the subjects DAS28’s evolution over time was fitted with a simple linear model and then the mean and 95% CI of the slope and p-values was presented. For this analysis, it were only used observations from the first 6 months to take advantage of the approximate linearity of the period after the start of the drug. Anakinra was not considered because of the small number of observations.

Incidence rates and incidence ratios with 95% confidence intervals (CI) were calculated for the time to remission (dataset A).

The proportion of subjects that remain event/outcome free was estimated using the Kaplan-Meier (KM) method and stratified Cox Proportional Hazards (Cox PH) regression was used assess for potential predictors of remission, adjust for confounding variables and estimate hazards ratios with 95%CI.

Hazards proportionality was assessed using the Grambsch-Therneau test of trend in Schoenfeld residuals for each covariate and also with the global version of this test available using the cox.zph function of the survival package [2].

Model selection was made by including 25 of the most relevant variables in the model and subsequently remove the one of the variables according with four different criteria.

These 25 variables were: therapy, sex, descent, disease duration, weight, height, season, age RA onset, erosive indicator, ESR, CRP, RF, age, SJC, TJC, extra articular manifestations, patient VAS, pain VAS, doctor VAS, DAS28, SDAI, HAQ, years of education, DMARD(s) indicator and biologic number. Cox regression was stratified by the biologic number.

The first criterion was to remove the least significant variable. The three other criteria consisted of removing the the variable that will produce the best model according with a measures of quality of the statistical models used for model selection. This measures were the Akaike information criterion (AIC), AIC correction for finite sample sizes and the Bayesian information criterion (BIC). To evaluate each adjustment it was calculated the Cox and Snell pseudo coefficient of determination (R-squared). The therapy variable was forcibly kept in the models even if removing it would produce a better model.

Recurrent remissions were analyzed using the Andersen and Gill (AG) conditional model with counting process independent increment model, the Prentice, Williams and Peterson (PWP) conditional model with counting process

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1 A counter for the number of biologics until the present one.
(CP) and gap time (GT) time scales, the Wei, Lin and Weissfeld (WLW) [5] marginal model and the total time-restricted (TT-R) [6].

On this models the coefficients are estimated ignoring the existing correlation between the events and the correction for the dependency is done by estimating a corrected variance, similar to the sandwich estimator. With the exception of the AG model, all other models were stratified by the biologic number and remission number

In our case time at risk is discontinuous because makes no sense that while on remission periods the subjects are at risk of being in remission.

The remission criterion used in this work was the American College of Rheumatology (ACR) and European league against rheumatism (EULAR) criterion for clinical trials (SDAI$\leq 3.3$) [7]. The reference for the biological therapies was etanercept, the most frequent one. The significance level ($\alpha$) used in this work was 0.05 (5%) calculated with two-sided tests, both for p-values and CI.

All statistical analysis in this work was conducted with the use of the statistical software R [8]. The dplyr package helped with the data processing and most of the figures and tables were made using ggplot2 and xtable package, respectively [9–11]. The survival analysis was performed using R’s survival package [12, 13].

3 Results

3.1 Descriptive analysis

For a total of 343 subjects with complete cases, there was 70.3% were RF positive, 69.7% were anti-CCP positive and 85.4% were women. From 366 subjects with reported race, 87.7% were white of European origin, 6% were black, 3.6% mulatto, 1.6% of non-European origin and the rest of Asian origin.

The hands distribution of the most affect joints in Figure 2 was made with a total of 348 subjects at the baseline of the first biologic. The results showed that the joints were more likely to be swollen (or inflamed) than tender (or painful) even if the proportions were sometimes very similar. In proportion, the wrists joints were the most affected with 59.4% and 51.7% of the subjects with swollen joints and 55.9% and 46.4% with tender joints, right and left wrist respectively.

Globally, the hands were the most affected area in the body. The most affected joints in the hand were the second and third metacarpophalangeal. As expected, the results are practically symmetric with a slight increased prevalence on the right side. The joints more times reported as not assessable were the right and left knees joints, 1.59% and 1.3%.

![Figure 2](image)

**Figure 2:** Hands distribution of the swollen (light red) and tender (red) joints at baseline.

\[2\text{counter of the number of the number of the risk-intervals/remissions per subject.}\]

In the LOESS estimate of Figure 3 it was observed that most of the DAS28 variation happened during the first year. On a closer look, it seems that the bulk of the change occurs between the third and sixth month and on this interval the observed DAS28 estimate implies, on average, a linear trend.

![Figure 3](image)

**Figure 3:** DAS28 by drug, over the 4 years follow-up period. Top left corner: Local Regression (LOESS) estimation of the mean DAS28 in time by biological therapy. Top right and bottom left corner: Estimate of the proportion of each drug by DAS28 value at 3 and 6 months. Bottom right corner: Cumulative distribution function for the 4 years follow-up time.

During this 4 years, the figure shows a similar behavior for all the the anti-TNF biological therapies, with the 95% confidence bands overlapping. Excluding the groups with anakinra and rituximab, the intercepts of rest of the drugs are not significantly different and were approximately 5.1 DAS28.

The right top and bottom left corner plots can be interpreted as prevalence estimates for the different DAS28 values given the biologic drug and over a period of two months centered at 3 and 6 months, respectively. We can observe that tocilizumab was more frequent for DAS28 values below 2.6 at 3 and
6 months of follow-up, while the DAS28 of the other drugs was more frequent for values above 5.1.

An overall interpretation of Figure 3 suggests that abatacept, anakinra and rituximab behave worse than the rest of the drugs and suggests that the anti-TNF have similar responses. Tocilizumab, the IL-6 receptor antagonist, presents the best results on all estimates and it is below the threshold for remission of DAS28 score after the 6 months of therapy.

![Figure 3](image3)

**Figure 4:** Disease activity (DAS28) conditional density estimate for the period of 4 years after the start of the therapy.

Figure 4 shows the evolution of the disease activity for each of the drugs. The estimates are a representation of the probability density estimates for each drug during the period of 4 years after the start of the therapy. They show how the prevalence for the different disease activity cut-points behaves over time for each of the drugs and they seem to be in accordance with the ones in Figure 3.

As can be seen, the patients on the anakinra did not achieve remission, while the rituximab plot shows slow progression and slight improvement in comparison with the baseline. The disease activity fell faster on golimumab in comparison with the other anti-TNF (adalimuma, etanercept and infliximab) and the patients that experienced a faster and more expressive improvement were the ones on the tocilizumab group. For this drug the proportion of high disease activity patients plummet to almost 0% in less than 6 months.

3.1 Summary measures analysis

Regarding the estimates for the analysis of the summary measures, it was found a significant difference between the estimated mean values of the initial DAS28 of the different drugs (P = <0.001). The mean difference in DAS28 after one year was larger for tocilizumab (Slope, -9.2, 95% CI, -12.00 to 6.40). The smallest decrease in DAS28 after a year occurred for abatacept. After accounting for sample variability the decrease with abatacept was not significant (Slope, -1.46, 95% CI, -3.86 to 0.93).

The proportion of significant slopes was larger for tocilizumab for a level of significance of 5%. 31.43% of the subjects on tocilizumab had statistically significant slopes. Rituximab was the next therapy with more significant slopes and had less than half of the number of significant differences compared to tocilizumab (14.29%). The estimates for adalimuma's slopes were only 5.26% of the times statistically significant. There was a statically difference between all the estimates for the percentage of significant slopes (P=0.049).

3.2 Cox regression analysis

On the time to remission data (dataset A), 146 remissions were observed (IR, 23.15 per 1000 person-months, 95% CI, 19.4 to 26.9); of these, the best results occurred for subjects on therapy with tocilizumab (30 remissions, IR, 60.56 per 1000 person-months, 95% CI, 38.52 to 82.60) and the worse results for the anakinra cohort, on which were not observed remissions. Additionally, the remission rate for rituximab, the second worst result, was 9.24 and could be as small as 4.01 and as large as 14.46 per 1000 person-months.

The 51 subjects on tocilizumab had a greater chance of remission when compared to the other 91 subjects on the etanercept (reference group). After accounting for sampling variability, tocilizumab therapy could increase the possibility of remission compared with patients enrolled on the reference drug from 36% to 240%, at the population level (IRR, 2.15, 95% CI, 1.36 to 3.40). Because these results are unadjusted there is the possibility that they are confounded.
The 55 subjects on rituximab had a smaller chance of remission when compared to the other 91 subjects on etanercept. After accounting for sampling variability, rituximab therapy had 83% to 40% smaller chances of remission than the patients enrolled on the reference drug, at the population level (IRR, 0.32, 95% CI, 0.17 to 0.6).

Subjects in the infliximab group had 17% smaller chances of remission in the follow-up period when compared to the subjects in the reference group. After accounting for sampling variability between this two anti-TNF drugs, however, there is no evidence that infliximab was better than etanercept at the population level (IRR, 0.83, 95% CI, 0.51 to 1.35, includes 1).

**Figure 6:** Kaplan-Meier estimate for remission by biological drug.

Figure 6 shows the KM curves for the dataset A used in the Cox regression. It can be seen that the curves for abatacept and golimumab crossed the others curves and there were no remissions for anakinra. The intersection of the survival curves was an indication of non-proportionality of the hazards. However, these curves were estimated with few observations and the intersection of the curves could be associated with the larger uncertainty of the estimates for a small sample and not be meaningful of non-proportionality.

The etanercept curve overlaps with the infliximab curve during the first two years and the golimumab curve overlapped with the adalimumab curve during the first year. At the end of the first year, 50% of the patients on tocilizumab already reached remission. The log-rank test gave a significant difference between the Kaplan-Meier estimates (P < 0.001).

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**3.2.1 Model Selection**

Figures 7 show the evolution of the AIC, AICc and BIC values during the backward elimination for each one of the criteria. Subjects on anakinra were excluded from the data because there were no remissions.

The figure show that most of the criteria produced the same results. Concerning the scores, it can be seen that the AICc asymptotically converges for the AIC values when the number of parameters decreases in relation to the number of observations. In addition, the minimum of the BIC score happens for a models with slightly less covariates than for the AIC and AICc score.

Table 1 presents the best set covariates accordingly with the criteria defined for variable elimination. The models for AIC and AICc are grouped because the minimum for these scores resulted from the same set of covariates.

Comparing the best models for dataset A, the BIC model does not have the ESR and the patient self-assessment VAS but the direction of association of the estimates agree between the two models. The global Grambsch-Therneau test of trend in Schoenfeld residual failed to reject the null hypothesis of PH for both models.

The estimates for adalimumab and rituximab were statistically significant for both models. The subjects on adalimumab were 73% less likely to achieve remission (HR, 0.27, 95% CI, 0.10 to 0.69, P=0.007) and the ones on rituximab had 88% less chances of remission than the reference group (HR, 0.12, 95% CI, 0.03
Table 2: Cox Proportional Hazards models for recurrent events. Prentice, Williams and Peterson (PWP) conditional model with counting process (CP) and gap time (GT) time scales. Wei, Lin and Weissfeld (WLW) marginal model. Total time-restricted (TT-R)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Dataset A (n=124)</th>
<th>Dataset A (n=124)</th>
</tr>
</thead>
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<tr>
<td><strong>Biologic</strong></td>
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<td></td>
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<tr>
<td>Etanercept</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Abatacept</td>
<td>1.22 (0.48-3.13)</td>
<td>0.90 (0.38-2.15)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>0.40 (0.21-0.77)**</td>
<td>0.39 (0.23-0.68)**</td>
</tr>
<tr>
<td>Golimumab</td>
<td>1.27 (0.56-2.85)</td>
<td>1.10 (0.54-2.22)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>1.00 (0.58-1.69)</td>
<td>0.79 (0.51-1.20)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>0.29 (0.13-0.68)**</td>
<td>0.28 (0.12-0.63)**</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>1.45 (0.86-2.45)</td>
<td>1.01 (0.63-1.62)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>0.97 (0.94-0.99)*</td>
<td>0.98 (0.96-1.01)</td>
</tr>
<tr>
<td>Weight</td>
<td>0.98 (0.97-1.00)*</td>
<td>0.98 (0.97-1.00)*</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.98-1.00)</td>
<td>0.99 (0.98-1.00)</td>
</tr>
<tr>
<td>ESR</td>
<td>1.00 (1.00-1.01)</td>
<td>1.01 (1.00-1.01)*</td>
</tr>
<tr>
<td>Patient VAS</td>
<td>0.99 (0.98-1.00)*</td>
<td>0.99 (0.98-1.00)*</td>
</tr>
<tr>
<td><strong>R²</strong></td>
<td>0.20</td>
<td>0.11</td>
</tr>
<tr>
<td>AIC/BIC</td>
<td>1402.66/1446.46</td>
<td>1072.49/1116.29</td>
</tr>
<tr>
<td>Global PH test</td>
<td>0.0730</td>
<td>0.0180</td>
</tr>
</tbody>
</table>

Table 1: Best models obtained for dataset A.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Dataset A (n=124)</th>
<th>Dataset A (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Abatacept</td>
<td>1.24 (0.23-5.38)</td>
<td>0.98 (0.22-5.38)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>0.27 (0.10-0.64)**</td>
<td>0.24 (0.09-0.64)**</td>
</tr>
<tr>
<td>Golimumab</td>
<td>4.59 (0.21-102.44)</td>
<td>3.31 (0.20-55.90)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>1.13 (0.52-2.47)</td>
<td>1.28 (0.59-2.79)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>0.12 (0.03-0.59)**</td>
<td>0.14 (0.03-0.59)**</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>2.12 (0.89-5.06)</td>
<td>2.28 (1.00-5.19)*</td>
</tr>
<tr>
<td>Disease duration</td>
<td>0.92 (0.88-0.97)**</td>
<td>0.92 (0.88-0.96)**</td>
</tr>
<tr>
<td>Weight</td>
<td>0.96 (0.94-0.98)**</td>
<td>0.96 (0.93-0.98)**</td>
</tr>
<tr>
<td>Age</td>
<td>0.97 (0.94-0.99)**</td>
<td>0.97 (0.95-0.99)**</td>
</tr>
<tr>
<td>ESR</td>
<td>1.01 (1.00-1.02)</td>
<td>1.00 (0.99-1.01)</td>
</tr>
<tr>
<td>Patient VAS</td>
<td>0.98 (0.97-1.00)*</td>
<td>0.99 (0.98-1.00)*</td>
</tr>
<tr>
<td><strong>R²</strong></td>
<td>0.41</td>
<td>0.28</td>
</tr>
<tr>
<td>AIC/BIC</td>
<td>329.55/360.57</td>
<td>332.09/357.48</td>
</tr>
<tr>
<td>Global PH test</td>
<td>0.8807</td>
<td>0.7765</td>
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</table>

to 0.58, P=0.008), for the AIC/AICc models.

Regarding the tocilizumab group, they were 112% more likely to achieve remission than the ones on etanercept. After accounting for sample variability this results were not statistically significant at the population level (HR, 2.12, 95% CI, 0.86 to 5.06, P=0.091). However, for the BIC model the effect of tocilizumab was statistically significant (HR, 2.28, 95% CI, 1.00 to 5.19, P=0.0495).

The results show that the chances of remission decrease 8% with each year of RA (HR, 0.92, 95% CI, 0.88 to 0.97, P=0.001). A weight increase of one kilogram represents a 4% decrease of the chances of remission (HR, 0.96, 95% CI, 0.94 to 0.98, P<0.001) and each year extra of age makes remission 3% less likely (HR, 0.97, 95% CI, 0.94 to 0.99, P=0.003).

The ESR covariate was positively associated with remission. An increase of one millimeter per hour at baseline makes remission 1% more likely (HR, 1.01, 95% CI, 1.01 to 1.02, P=0.092).

The effect of the patient global assessment VAS at baseline was of reducing the chances of remission (HR, 0.98, 95% CI, 0.97 to 1.00, P=0.026).

### 3.2.2 Recurrent events analysis

![Figure 8: Kaplan Meier estimate for recurrent events.](image-url)
to the first four due to the short amount subjects. Assuming that the time for a recurrent remission is independent, there was a significant difference between the KM curves (P<0.001).

From 368 records, 146 achieved remission and 125 relapsed. From these 125 relapses, 62 subjects eventually had a second remission. While the median time for the first remission was almost three years (Median, 2.88, 95% CI, 2.21 to 3.47 years), the median time for the second remission was nine months (Median, 9.41, 95% CI, 8.32 to 16.81 months). It is possible to observe that KM estimates are ordered regarding the time to remission and the remission number. The first remission is the one that takes longer to achieve, and progressively, from the second to the fourth remission, the time to the event gets shorter.

The HR estimates for the biological therapies (Table 2), were significant for adalimumab and rituximab. This had already happened for other models with dataset A (Table 1), but on this models the tocilizumab estimates were not significant. However, the direction of association for this therapies and golimumab comparing to etanercept was the same between recurrent remissions models and first events models. In relation to infliximab and abatacept, the estimates for the first were not consistent to the other models and the HR of the second fluctuated around one between models.

For the PWP-GP model, patients on adalimumab were 50% less likely to achieve remission than if they had enrolled on etanercept (HR, 0.41, 95% CI, 0.23 to 0.73, P=0.002). In addition, patients on rituximab were 68% less likely to achieve remission (HR, 0.32, 95% CI, 0.14 to 0.72, P=0.006) and patients on tocilizumab were 26% more likely to achieve remission (HR, 0.32, 95% CI, 0.77 to 2.05, P=0.352) both relative to the effect of etanercept.

The disease duration, weight, age, ESR and patient VAS had results very similar to the previously obtained estimates. An increase of one unit of disease duration or age reduces the chances of remission by 2%. It is also more difficult for older patients with a higher patient VAS at baseline to achieve remission. Nevertheless, higher ESR at baseline increased the chances of remission (HR, 1.01, 95% CI, 1.00 to 1.01, P=0.064) like it was already seen in estimates of other models.

4 Conclusion

The investigation on EMR data from Reuma.pt register was able to extract important information about the sample and contributed the base knowledge about biological therapies for RA in clinical-practice. It was found the best set of predictors for dataset A and the estimates from different models were compared.

The proportion of women on this sample of Reuma.pt was almost 6 times greater than of men. However, the prevalence for women is estimated to be two to three times higher than in men and in Portugal this proportion is 4:1 [14, 15]. This probably happened because there was more women failing the conventional therapies than men. Regarding RF and anti-CCP, there was about 2 times more patient with it than without. This values are similar to the prevalences found in the general population [16].

The observation of anatomical distribution of the swollen and tender joints at baseline showed that a joint was more likely to be swollen than tender, the distribution is almost symmetric as expected in RA and the wrists and the hands joints are the most affected. In the hands, the second and third metacarpophalangeal joints were the most affected.

The results show that most of the disease activity variation occurred for the first 6 to 12 months after the therapy start.

Given the consistence of the results regarding the anti-TNF drug and the lack of significant difference in treatment effects between anti-TNF drugs, the descriptive analysis suggests that this drugs are equivalent.

The systematic technique used for model selection was simpler and easier way of selecting covariates than trying all possible combinations of covariates. The strikingly lower DAS28 and higher frequency of remission among patients on tocilizumab in our data and across different models suggests an important effect of this drug on the reduction of the RA activity and remission induction. This results reinforce the relevance of the IL-6 as pro-inflammatory cytokine in RA.

Subject on anakinra had no remissions and rituximab and adalimumab were less efficacious comparing to etanercept. For recurrent events, it was found that for half the subjects the time for the first remission can be 3.67 times greater than the time for the subsequent remissions. It was also observed that the mean remission-time decreases for every new remission.

To conclude, this study has developed a general methodology for the representation and analysis of Reuma.pt data. It has been demonstrated that some therapies are significantly more efficacious than others and that the time since the onset of the disease, age and weight affect the chances of remission. Further methods should be applied and this data can will be subject of more research.

4.1 Limitations

A limitation of this work was the non-existence of a clear reference group for the therapies, like a placebo group or group only not on biological therapies.

In the case that the hazard of a predictor changes over time and the hazards proportionality does not hold, some authors considered that the estimate can
be interpreted had the average HR over the follow-up time [2] [17].

A disadvantage of working with real-world data is the lack of control of the sampling procedure. In our case, there was selection bias of both patients and therapy and the data was also convenience sample.

4.2 Future Work

This work can be used as a guide for future work on Reuma.pt and the estimates might be useful to design future studies and to compute the sample size for a desired statistical power. As is known, preliminary observational studies are first done to develop evidence for the possibility of doing larger and perhaps more costly randomized trials.

In addition, the covariates from the selected models can be later be used for future models and prediction of the hazards in new data.

Some of the therapies in this work did not have a cost-effectiveness study because it was not mandatory at the time they were authorized in the market in Portugal. Namely, adalimumab, anakinra, etanercept, infliximab and rituximab. Given the high costs of biologic therapies and the results of this work, future work should be done to analyze the cost-effectiveness of these medications.

References


