**INTRODUCTION**

Rheumatoid Arthritis (RA) is a chronic systemic autoimmune disease predominantly characterized by chronic inflammation of synovial joints. Without appropriate therapy the disease almost inevitably leads to severe joint deformities, particularly of the hands, chronic pain and suffering, disability, inability to work, poor quality of life and early mortality.**1** Chronic glucocorticoids and non-steroidal anti-inflammatory drugs used from the 1950´s failed to control disease and had too many associated side-effects, often life-threatening.**2** The era of innovative medicine occurred in the late 1990’s with the focus shifted to a treat to target–based approach, with new treatment paradigms, including early diagnosis and an intensive management approach. This was made possible through the use of biotechnological disease-modifying anti-rheumatic drugs (bDMARD) in addition or as an alternative to synthetic disease-modifying anti-rheumatic drugs (sDMARD).**3,4,5** The first biological therapies to be developed in rheumatology were the tumor necrosis factor inhibitors (TNFi) for patients who failed treatment with sDMARDs.**4,6** Most importantly, the therapeutic judgment has to take into account co-morbidities (such as heart failure and infectious risk), past history of neoplasia and ideally identify those with a high risk of relapse.**6** Currently there is a much wider therapeutic armamentarium ranging from membrane receptor agonists or antagonists (Fc-CTLA4, CD20), anti-cytokine (Il-6, IL-17) to JAK kinase inhibitors.**7**

Despite advances there are still no easily assessable bio-markers to establish a personalized treatment approach at the time of disease onset or diagnosis. Similarly, during follow-up most therapeutic decisions frequently remain empirical. This is the case when tentatively adapting the chosen therapy to a personalized optimal dose and regimen, but also when prescribing co-therapies or switching to other bDMARD when the treatment is inefficient, or associated with intolerance or adverse events. Furthermore, therapies may be ineffective (wrong target) or become neutralized due to their immunogenicity. Of note, in Portugal, these therapies are entirely state subsidized and are associated with a significant societal cost.

Clinical assessment of disease activity, progression and remission are robust and quantitative, as are indicators of patient’s quality of life. In this work we aimed to study every single patient with RA that ever received biological therapy in our Unit and answer some very simple questions that nevertheless remain at the core of the major investment for these patients. Are our patients free of deformities? Are they able to work and do they lead productive lives? Have they retained their original therapies? Was a switch required? Was therapy interrupted and for what reason? Have they suffered important side-effects? Do they suffer from important co-morbidities? Have we lost patients to follow-up? Are they alive?

**MATERIALS AND METHODS**

**1. STUDY DESIGN AND POPULATION**

This is a cross-sectional study that took place in an outpatient care setting between December 2017 and May 2018. We only included patients that were on biological therapy for at least three months. All fulfilled the American College of Rheumatology 1987**8** and 2010**9** revised criteria for the classification of Rheumatoid Arthritis (RA) and were aged ≥18 years. Our Unit´s database allowed us to identify 94 patients with RA that started biological therapy (bDMARD) from 01/2002 to 12/2017. At the time of recall, seven patients were lost to follow-up, six patients had died, and four refused to participate in our study. Overall, recall involved 77 patients. Each patient underwent a physical examination, recording of disease activity and hand joint deformities and was requested to complete a questionnaire regarding demographic and social characteristics as well as generic Health Related Quality of Life (HR-QoL) questionnaires validated for Portugal. Demographic and clinical data was also extracted from the medical records. The Charlson Comorbidity Index (CCI)**10** which predicts 10-year survival in patients with multiple comorbidities was calculated for all patients at onset of bDMARD therapy and at time of recall. Pharmacy refill information was obtained for every patient under self-administered biological therapy. The study was registered at EuroQol Group website (14th July 2013) and collaboration was obtained from Professor Pedro Lopes Ferreira (24th January 2015). The study protocol was approved by the hospital Ethics Committee (process 183/2015) and the Comissão Nacional de Protecção de Dados (3886/2016).

**2. THERAPEUTIC APPROACH**

In the latter years, a T2T approach was followed according to recommendations.**5** When an anti-TNFα patient was intolerant to methotrexate, failed to reach at least low disease activity or presented with poor prognostic signs, a switch was performed, to rituximab, tocilizumab or abatacept, depending on prior medical history and comorbidities and also according to marketing authorizations and ministry of health re-imbursement policies at the time. Rituximab was administered at the dose of 1 g, 2 weeks apart, with the exception of one patient with Sjögren´s syndrome that received 375 mg/m2 – 4 doses, weekly. Prednisolone was tapered and discontinued whenever possible.

**3. DISEASE ACTIVITY AND DEFORMITIES**

Disease activity was measured by Disease Activity Score 28-erythrocyte sedimentation rate [DAS28-ESR]**11** defined as follows: high disease activity (HDA) > 5.1; moderate disease activity (MDA) ≥ 3.2 and ≤5.1; low disease activity (LDA) ≥ 2.6 and < 3.2; remission < 2.6. DAS28-ESR was routinely recorded at clinic visits. In a subset of patients, at recall, the number of wrist and hand deformities was counted by the physician per patient.

**4. HEALTH ASSESSMENT QUESTIONNAIRE**

The functional status was measured by the health assessment questionnaire (HAQ). The HAQ consists of eight categories which evaluate the patient’s difficulty with activities of daily living over the past week. The questionnaire consists of 41 total items: 20 specific activities are grouped into 8 functional categories with each category given a single score equal to the maximum value of their component activities, 13 additional questions on the use of assistive devices, and 8 additional questions assessing help received from others using a scale 0, 1, 2 or 3. The patient's responses are made on a scale from zero (no disability) to three (completely disabled).**12-15**

**5. PATIENT COMPLIANCE**

Compliance was determined by the proportion of days covered (PDC) for the index biologic during the 12-month follow-up period. Non-compliance of self-administered biologics (etanercept adalimumab, golimumab and tocilizumab) was defined as proportion of days covered <80% during the post index period.**16** Patient compliance was obtained by using pharmacy refill information for the duration of one year prior to recall visit. Patients were considered non-compliant with medication when less than 80% of prescriptions were collected from the pharmacy. Patients under intravenous medication (rituximab, tocilizumab, infliximab, and abatacept) were considered compliant since administration of biologics is performed in the Outpatient clinic by qualified nurses.

**6. HEALTH RELATED QUALITY OF LIFE**

 HR-QoL is defined as those aspects of quality of life that directly or indirectly relate to health, a concept that includes physical, psychological, and social domains and was measured through the Short Form (SF-36) Health Survey and the EuroQoL Group 5D-3L (EQ-5D-3L).

 SF-36 is a 36-item, patient-reported survey consisting of eight scaled scores, which are the weighted sums of the questions in their section. Some questions have an inverted scale. After each scale is directly transformed into a 0-100 scale, the lower the score the higher the disability, in other words, a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability. The eight dimensions are: vitality (V), physical functioning (PF), bodily pain (BP), general health perceptions (GH), physical role functioning (RP), emotional role functioning (RE), social role functioning (SF) and mental health (MH). Scoring algorithms allow for aggregating scores from the eight SF-36 subscales in two distinct scores: a Physical Component Summary (PCS) and a Mental Component Summary (MCS). The global health transition question (HTQ) asks respondents to rate their general health compared with 1 year ago, with five categories of response: ‘much better,’ ‘somewhat better,’ ‘about the same,’ ‘somewhat worse’ and ‘much worse. In the present study SF-36 was standardized according to the norms for the Portuguese population.**17,18**

Each patient was asked to report their socio-demographic characteristics (age, gender, marital status) and complete the EQ-5D-3L in order to self-report their own health in a five-dimension descriptive system (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each attribute has three levels: no problems, some problems, and severe problems, resulting in 243 possible health states, the best of which corresponds to a score of 1. Each health state was then assigned an index value by applying scores from national Portuguese preference weights (tariffs) using a validated model.**19,20** Indicated on a Visual Analogue Scale (VAS) range from with endpoints 0 for the ‘‘worst imaginable health state’’ to 100 for the ‘‘best imaginable health state’’.

**7. Statistical analysis**

According to distribution normality continuous variables were recorded as means (± standard deviation) or medians (IQR1 - IQR3) and comparisons were made using the Mann-Whitney test. Dichotomous variables were examined by frequency distribution, recorded as proportions, and comparisons were made using the Chi-squared test or Fisher’s exact test for independent samples. The Wilcoxon Signed Rank test was used to compare paired means for continuous data that were not normally distributed. Correlations between continuous and nominal variables were analysed with Pearson's or Spearman´s correlation coefficient, respectively. Only moderate correlations (Spearman rho values <0.40) were considered for the regression model. Nominal two-sided p values of <0.05 were considered statistically significant. Analyses were performed using SPSS version 23.

**RESULTS**

**Result 1. Initial Patient Cohort: demographic and clinical features**

Overall 94 patients started bDMARD in their fifth decade of life, after a median disease duration of four years (Table I). The majority of patients were female and significantly younger than the male counterpart at bDMARD onset (p=0.038). There were no other differences between the types of bDMARD as regards gender attribution (Supplementary Table I). Rheumatoid factor or anti-CCP antibodies tested positive in 81% of the patients. The first patient started bDMARD in 2002. Methotrexate (MTX) - median dose 20 mg per week and corticosteroids - median dose prednisolone (PDN) equivalent 10 mg/day had failed to control disease activity in 87% and 66% of patients, respectively. Treated dyslipidemia and arterial hypertension were frequently documented, 10% of patients were obese and 16% were smokers. The Charlson comorbidity index estimated a median 10-year survival of 90%.

**Result 2. Recall Patient Cohort: demographic and clinical features**

Recruitment was achieved in 77 patients, the majority of whom between 47 and 66 years of age (table II). However, as regards professional status almost half of the population was in retirement (49%) and 28% were unemployed. The majority (40.8%) only had 4 years of schooling; 11% had completed 12 years of schooling and 17% underwent a university education, the latter three times more frequent in men. Only 17% were single.

Over two thirds (79%) of the patients remained on bDMARD (n=61), the majority of whom were on etanercept and tocilizumab; 75% remained on the original bDMARD with an adequate compliance (Table III). Approximately one fifth of the patients stopped bDMARD (n=16), mostly due to infection but also because of primary or secondary failure or wilfully due to subjectively controlled disease activity. One third of patients (n=22) switched from the original bDMARD, 14 having required further switches. Maximal number of 3 and 4 switches occurred in single patients. After bDMARD onset, MTX use reduced from 95 to 22% (p=0.002, Chi square test between frequencies). Likewise, steroid use significantly decreased from 74 to 30%, (p<0.001, Chi square test between frequencies), halving the prednisolone equivalent dose to a median of 5 mg/day. Of note, the frequency of steroid use was slightly higher in those patients that discontinued bDMARD. Approximately 40% presented hand deformities, but the median number of deformities per patient was generally very low. Smoking, obesity, chronic anxiety and depression were only registered in females while dyslipidemia and arterial hypertension were equally distributed among the participants. The original age difference between males and females was no longer present, with no other difference between sexes as regards demographic features, disease duration from diagnosis to recall, onset of first bDMARD and follow-up. Unlike before, the Charlson comorbidity index was now higher in man than women, estimating a lower 10-year survival for the former (p=0.019) (Supplementary Table II).

At recall, DAS28-ESR and HAQ were significantly lower when compared to the pre-bDMARD values, both with a p value <0.001, [CI -2.56 to -1.6 and -1.04 to -0.533) respectively (Wilcoxon Signed Rank test)]. However the recall median DAS28-ESR of 3.2 (IQR 2.390 – 3.950) was borderline between low and moderate disease activity, irrespective of current bDMARD therapy (p=0.917 Mann Whitney-U test - MWU). The median HAQ-DI index at recall was 1.310 (IQR 0.500 – 1.810) similarly indicative of mild to moderate disability and best correlated to pre-bDMARD HAQ. Of note, the pre-bDMARD HAQ could only be obtained for 28 of the 77 patients at recall.

Recall disease activity measured by DAS28 was significantly determined by pre-bDMARD DAS28, number of deformities per patient and number of patients on steroids that had stopped bDMARD therapy (adjusted R2 0.9, p< 0.001), the latter contributing most significantly to recall disease activity. Recall functional impairment measured by HAQ was only moderately positively correlated with pre-bDMARD HAQ (r=0.563, p=0.002) and negatively moderately correlated to SF-36 HR-QoL indices (PCS and MCS) and EQ-5D-3L VAS. Other than the correlation between age, duration of disease and follow-up and besides the Charlson morbidity index (r=0.7, p=0.001, Pearson correlation), there were no other strong correlations between continuous variables at recall (Supplementary Table IV). Spearman correlations between clinical parameters revealed that retention of the original bDMARD was positively correlated with the duration of bDMARD therapy (r=0.412, p=0.001), positively with pre-DMARD MTX use(r=0.4, p<0.001), yet negatively to recall MTX (r=-0.9, p<0.001). MTX dose at recall was in turn negatively correlated to the number of switches per patient (r=- 0.5, p=0.02) as well as to bDMARD discontinuation/on steroids (r=- 0.9, p=0.04) (Supplementary Table V – only moderate and strong significant correlations are shown).

**Result 3. Recall Patient Cohort: HEALTH RELATED quality of life outcomes**

Due to missing values, the SF-36 Physical (PCS) and Mental Component Summaries (PCS) could only be calculated for 44 subjects with mean values of 37,7 ± 9,5 and 46,5 ± 11,6, respectively. Lower scores on the SF-36 reflect poorer HR-QoL, particularly affecting the physical domains, general health perception and vitality in our patient cohort (Figure 1). There were no significant differences between men and women other than in the health transition domain, where men fared better than women as regards feeling somewhat better than the year before (p=0.02) (Supplementary Table VI). Regarding EQ-5D-3L (Table III), the mean calculated score and VAS were 0,45 (± 0,3) and 60,64 (± 22,1), respectively.

With the exceptions of HAQ disability index and other than a strong correlation between the EQ-5D-3L and EQ-5D-VAS and moderate correlations between these and the MCS and PCS, there were no significant correlations between HR-QoL indices and clinical variables (Supplementary Table IV), with respect to the professional situation, schooling or marital status (Supplementary Table VII). Even though it did not reach statistical significance, unemployed patients had a higher DAS28, HAQ, and number of deformities, with the lowest EQ-5D-3L score.

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**Result 4. Demographic, clinical and therapeutic characterization of patients who died or were lost to follow-up**

Patients lost to follow-up were younger than the group as a whole, emigrated or returned to their country of origin or followed their physician to another hospital center (Table IV). The deceased patients had a statistically significant lower estimated 10-year survival rate at the time of first biologic therapy (p=0.006) and discontinued bDMARD at a higher frequency (p=0.028) than the recall patients (Supplementary Table VIII).

**DISCUSSION**

Our Unit is dedicated to the treatment of patients with systemic autoimmune diseases including RA. We officially started treating RA patients with biological therapy in 2002, our first patient ongoing regular follow-up since treatment onset. Pre-bDMARD onset, despite sDMARD therapy, our patients, with a median age of 50 years, initially presented with high disease activity (median DAS28 of 5.30) and a high HAQ disability index (median 2.00). These indices are known to be inter-related and long known to predict irreversible damage, physical and work disability and mortality.**21-23**

In our cohort, a high risk group of patients, with a potentially productive work-life, initiation of bDMARD occurred at a median of four years after RA onset. This diagnostic/therapeutic delay merits further discussion. A recent meta-analysis of 36 randomized clinical trials comparing the standard doses of the five anti-TNF inhibitors combined with MTX to MTX mono-therapy described trial participants with a mean age varying from 48.4 to 60.7 years and a mean duration of disease from 0.2 to 11 years,**24** effectively meaning that the median therapeutic delay of four years, in our patient population, is probably not that prolonged when compared to others. Lack of access to specialist care may significantly contribute to the therapeutic delay. The Portuguese register Reuma.pt provides longitudinal information for over 7000 patients with RA at a national level.**25** Patients' access to biologics in RA stood at 7% in 2010 (12 percentage points below the average of European selected countries)**26** having tripled from 2007 to 2012.**27** Low education, on the other hand, may contribute to poor health literacy (40.8% of our patients only had 4 years of schooling) but of note, the latter has also been found to be relatively common among those with a high level of education.**28**

Due to the retrospective nature of our study we are unable to assess the degree of irreversible joint damage already present at the time bDMARD was started. At recall, 22 of 54 patients presented hand deformities but the highest number of deformities per patient was 2.25. The number of deformities, which might have been prevented through earlier treatment, was actually an important predictor of disease activity at recall. Remission or LDA as determined by DAS28 was found in 51% of patients. Disappointingly, 37% of patients presented with moderate and 11% with high disease activity. DAS28 was also significantly determined by pre-bDMARD DAS28; uncontrolled disease activity being related to steroid use in patients no longer on bDMARD. Even though significantly lower, HAQ disability index continued to reveal severe functional disabilities. It should be highlighted that there was no relationship between the number of switches and recall DAS28 or HAQ.

In our study, after a median duration of 7 years, most patients (79%) remained on bDMARD, retaining the original medication (etanercept). Discontinuation of bDMARD occurred primarily due to infection (38%) followed by treatment failure (26%). Our data contrasts with that of the Rheumatic Diseases Portuguese Register (Reuma.pt) of bDMARD treated patients after 13 years of prospective follow-up where a higher frequency (50%) discontinued their first bDMARD principally due to inefficacy (55%) with a much lower frequency of infections (4 %).**29** In addition, and unlike in Reuma.pt, neither baseline HAQ nor the number of co-morbidities predicted bDMARD discontinuation; the Charlson co-morbidity index was however significantly higher in those patients who died.

When compared to the frequencies of employed Portuguese persons (pordata.pt - 2017), the majority of whom have been through more than four years of schooling, our group of patients may have been at a disadvantage. On the other hand the mean national age for retirement in Portugal in 2018 was 62.6 years, corresponding to the median age of our patients. Not unsurprisingly then, at recall, almost 50% of our patients were pensioners. The median age of the unemployed patients (57.5 years) was nearing retirement time but it should be noted that despite our efforts, they had the highest disease activity, functional impairment and the lowest EQ-D5-3L score. This is in line with a recent Portuguese study that recalled a similarly high HAQ value for unemployed albeit younger RA patients.**30**

The mean EQ-5D-3L calculated with the Portuguese tariff was 0,45 (± 0.3), effectively placing our RA patients at a low score as regards HR-QoL. There was no significant correlation to any clinical parameter. Interestingly, baseline mean EQ-5D-3L and HAQ values for a Greek population of RA patients were 0.57 and 0.75, (our values being 0.45 and 1.3) respectively, in which higher HR-QoL scores clearly correlated with a lower functional impairment as measured by HAQ. We nevertheless believe that our therapeutic strategies have provided benefit as evidenced by a decrease in disease activity and improvement in the disability index.

We consider the following limitations. Due to the retrospective nature of the study we could not assess H-QoL indices from baseline and as such could not assess the efficacy of particular drug regimens or compare them. As bDMARD therapy was started late in the course of disease, we cannot assess if those who started early attained added clinical improvement compared with patients with a delayed start of therapy. We could not assess how many patients became work-disabled due to disease. Moreover, the dynamic nature of RA therapy cannot be reflected in this cross-sectional design. Some of the patients who had moderate or high disease activity at the time of recall were switched to alternative therapies that proved effective; other patients that were controlled at recall later lost response.

**CONCLUSIONS**

The use of bDMARD provided therapeutic benefit as reflected by a significant decrease in DAS28, HAQ and steroid use. There were few hand joint deformities per patient. The presence of comorbidities had an impact on mortality. The majority of patients retained the original bDMARD, few switches were required and the major cause for bDMARD interruption was infection. Nevertheless the mean EQ-5D-3L scores were low, indicating a poor HR-QoL, the smaller impact on the mental component domains of SF-36 possibly invoking less suffering. Earlier onset of therapy may have prevented deformities and residual irreversible functional incapacity. Increased literacy, access to healthcare and new therapeutic choices can be expected to contribute to earlier diagnosis and remission and improved overall outcomes in the years to come.

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