Biological Therapy in Patients with Rheumatoid Arthritis in a Tertiary Center in Portugal: A Cross-Sectional Study

Artrite Reumatóide em Doentes Submetidos a Terapêutica Biológica num Centro Terciário de Referenciação em Portugal: Um Estudo Transversal

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ABSTRACT

Introduction: Clinical outcomes in rheumatoid arthritis have greatly improved with therapeutic advances. Despite the availability of substantial clinical trial evidence, there is a lack of real-life data. The aim of this study was to assess disease status and quality of life in an outpatient population treated with biological disease-modifying anti-rheumatic drugs.

Material and Methods: Cross-sectional study recalling all patients ever treated in our unit with biological disease-modifying anti-rheumatic drugs. Clinical and demographic data, compliance, disease activity, functional status, joint deformities, and comorbidities were documented, and patients queried on occupational status, education, marital status and generic health related quality of life questionnaires.

Results: Recall was attended by 77 of the original 94 patients. At recall, median age was 63 years old, 82% of the patients were female and the median disease duration was 12 years. Biological therapy was started at a median of four years following disease onset. According to the disease activity score (DAS28), the percentage of patients with high, moderate, low disease activity or remission changed from 50, 45, 0 and 5 (pre-therapy) to 11, 37, 25 and 26 at recall, respectively; functional status was significantly improved. Seventy-five per cent of the patients retained the original treatment with good compliance. Lower Short Form-36 domain scores accompanied a low EQ-5D-3L score. Deceased patients (n = 6) had a lower estimated 10-year survival rate. In this group, biological therapy was discontinued at a higher frequency during follow-up.

Discussion: A high disease activity and a high HAQ disability index characterized most patients at pre-bDMARD onset.

Conclusion: Despite therapy switches and regular follow-up, a significant percentage of patients still presented with moderate disease activity, functional impairment and a poor health-related quality of life.

Keywords: Arthritis, Rheumatoid/drug therapy; Biological Products/therapeutic use; Biological Therapy; Quality of Life

RESUMO

Introdução: Avanços no tratamento da artrite reumatóide contribuiram para uma evolução favorável. Apesar de evidências substanciais provenientes de ensaios clínicos, são menos conhecidos os dados provenientes da vida real. O objetivo do estudo foi caracterizar a doença e a qualidade de vida em doentes sob fármacos biotecnológicos.

Material e Métodos: Trata-se de um estudo transversal com recolha de dados clínicos relativos à adesão terapêutica, atividade da doença, capacidade funcional, deformidades articulares, comorbilidades e questionários de qualidade de vida relacionada com a saúde, estado civil, situação profissional e escolaridade.

Resultados: Foram recrutados 77 doentes do grupo original de um total de 94. A mediana da idade foi 63 anos, 82% do sexo feminino e início de biológico cerca de quatro anos após o início da doença, com uma mediana de duração de 12 anos. De acordo com o *Disease Activity Score* (DAS28), a percentagem de doentes com atividade alta, moderada, baixa ou em remissão mudou, respectivamente, de 50, 45, 0 e 5 pré- biológico para 11, 37, 25 e 26 na altura da re-avaliação, com melhoria funcional. Setenta e cinco por cento dos doentes mantiveram o tratamento original com boa adesão. Pontuações mais baixas do *Short Form-36* associaram-se a uma baixa pontuação no EQ-5D-3L. No grupo de doentes que viriam a falecer (n = 6), foi observada uma menor esperança de vida aos 10 anos, assim como uma maior discontinuação da terapêutica biológica.

Discussão: Pré-biológico, uma elevada percentagem dos doentes apresentava elevada atividade da doença e incapacidade funcional.

Conclusão: Não obstante ajustes terapêuticos e seguimento regular, uma percentagem significativa de doentes mantinha atividade moderada e limitação funcional com baixa qualidade de vida relacionada com a saúde.

Palavras-chave: Artrite Reumatoide/tratamento farmacológico; Biológicos/uso terapêutico; Qualidade de Vida; Terapia Biológica

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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 medicines occurred in the late 1990's with the focus shifting to a treat to target–based approach (T2T), with new treatment paradigms, including early diagnosis and intensive management. This was made possible through the use of biological disease-modifying anti-rheumatic drugs (bDMARD) in addition or as an alternative to synthetic disease-modifying anti-rheumatic drugs (sDMARD).[3-5] The first biological therapies to be developed in rheumatology were tumor necrosis factor inhibitors (TNFi) for patients who did not respond to 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) to anti-cytokine (Il-6, IL-17) and JAK kinase inhibitors.[7]

Despite advances, there are still no easily available biomarkers to establish a personalized treatment plan 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 another 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,[8] as are indicators of a patient's quality of life. In this study we aimed to assess 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 management of 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?

MATERIAL AND METHODS

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 patients fulfilled the American College of Rheumatology 1987[9] and 2010[10] revised criteria for the classification of rheumatoid arthritis (RA) and were aged 18 years and over. Our unit´s database allowed us to identify 94 patients with RA that started biological therapy (bDMARD) from January 2002 (date of first bDMARD treatment in the unit) to December 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, the 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[11] which predicts 10-year survival in patients with multiple comorbidities was calculated for all patients at the onset of bDMARD therapy and at the 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).

Therapeutic approach

In the latter years, a T2T approach was followed according to recommendations.[5] When a TNFi 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, two weeks apart, with the exception of one patient with Sjögren´s syndrome that received 375 mg/m^2 – four doses, weekly. Prednisolone was tapered and discontinued whenever possible.

Disease activity and deformities

Disease activity was measured by Disease Activity score 28-erythrocyte sedimentation rate [DAS28-ESR][12] 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 attending physician counted the number of wrist and hand deformities per patient.

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 eight functional categories with each category given a single score equal to the maximum score of their component activities, 13 additional questions on the use of assistive devices, and eight additional questions assessing help received from others using a scale 0, 1, 2 or 3. The patient's responses were recorded on a scale from zero (no disability) to three (completely disabled).[13-16]

Patient compliance

Compliance was determined by the proportion of days covered (PDC) for the index biological drug 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.[17] 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 in our Unit qualified nurses perform administration of biologics in a Day Hospital.

Health related quality of life

HR-QoL, defined as those aspects of quality of life that directly or indirectly relate to health, a concept that includes physical, psychological, and social domains, 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 converted 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 aggregation of scores from the eight SF-36 subscales in two distinct scores: a physical component summary (PCS) and a mental component summary (MCS). In the present study, SF-36 was analysed according to the norms for the Portuguese population.[18,19]

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/depres-sion). 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 one. Each health state was then assigned an index value by applying scores from national Portuguese preference weights (tariffs) using a validated model,[20,21] Patients were asked to provide a score on a visual analogue scale (VAS) ranging from endpoints 0 for the 'worst imaginable health state' to 100 for the 'best imaginable health state'.

Statistical analysis

According to the normality of their sampling distributions, continuous variables were recorded as means (± standard deviation) or medians (IQR1 - IQR3). Dichotomous variables were examined by frequency distribution, recorded as percentage, and comparisons were made using the chi-square test or Fisher's exact test for independent samples. The t test was used for comparison between normally distributed variables. For continuous data that were not normally distributed, the Wilcoxon Signed Rank test was used to compare paired means and the Mann-Whitney U test for comparisons between independent samples. Correlations between continuous variables were analysed with Pearson's correlation coefficient. A p value below 0.05 was considered statistically significant. Analyses were performed using SPSS version 23 software.

RESULTS

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 1). Most patients were female with no differences between the types of bDMARD regarding age and gender distribution (Appendix 1, Table 1; see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13605/Appendix_01.pdf). Rheumatoid factor or anti-CCP antibodies were positive in 81% of the patients. 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 (51%) and arterial hypertension (41%) were frequently documented, 19% of patients suffered from chronic anxiety, 16% were smokers and 10% were obese. The median of the estimated 10-year survival using the Charlson comorbidity index was 90%.

Recall patient cohort: demographic and clinical features

Recruitment was achieved in 77 patients, mostly between 47 and 66 years of age (Table 2). Regarding professional status almost half of the sample was retired (49%) and 10.5% unemployed. The majority (40.8%) only had four years of schooling; 11% had completed 12 years of schooling and 17% underwent university education. Only 17% were single.

Over two thirds (79%) of patients remained on bDMARD

Table 1 – Baseline demographic and clinical characteristics

	Original cohort	Recall cohort
Number of patients	94	77
Male:female	19:75	14:63
Caucasian, n (%)	86 (91)	71 (92)
Age (y), median (IQR)	50 (42 – 57)*	63 (55 – 71)
Age (y) bDMARD started, median (IQR)	56 (47 – 62)	56 (49 – 61)
Disease duration (y) from time of diagnosis to first bDMARD, median (IQR)	4 (1 – 9)	4 (1 – 9)
Either or anti-CCP/RF positive, n (%)	76 (81)	61 (79)
Anti-CCP/RF negative, n (%)	18 (19)	16 (21)
Prior to bDMARD:		
Prednisolone, n (%)	62 (66)	57 (74)
Prednisolone equivalent mg/day, median (IQR)	10 (5 – 12)	10 (5 – 10)**
Methotrexate, n (%)	82 (87)	73 (95)
Methotrexate mg/day, median (IQR)	20 (15 – 20)	20 (13 – 20)
Pre-bDMARD DAS 28 – ESR, median (IQR)	5.31 (4.51 – 6,29)	5.060 (4.500 – 5.998)
Number of patients for which DAS available	75	62
- high disease activity (HDA) > 5.1, n (%)	52 (46)	31 (50)
- moderate disease activity (MDA) ≥ 3.2 and ≤5.1, n (%)	30 (40)	28 (45)
- low disease activity (LDA) ≥ 2.6 and < 3.2, n (%)	0	0
- remission < 2.6, n (%)	3 (4)	3 (5)
Pre-bDMARD HAQ, median (IQR) initial n=33; recall n=27	2.00 (1.47 – 2.53)	2.00 (1.44 – 2.49)
On bDMARD, n (%)	94 (100)	61 (79)
bDMARD:		
Infliximab, n (%)	3 (3)	1 (1,5)
Etanercept, n (%)	55 (59)	31 (51)
Adalimumab, n (%)	14 (15)	5 (8)
Golimumab, n (%)	2 (2)	2 (3)
Rituximab, n (%)	6 (6)	6 (10)
Tocilizumab, n (%)	14 (15)	15 (25)
Abatacept, n (%)	0	1 (1.5)
Comorbidities:		
Benign tumors, n (%)	2 (1)	0
Malignancy	6 (6)	2 (2)
Active smoking, n (%)	12 (16)	11 (14)
Dyslipidemia, n (%)	48 (51)	41 (53)
Arterial hypertension, n (%)	39 (41)	33 (43)
Obesity, n (%)	9 (10)	8 (10)
Chronic anxiety/depression disorder, n (%)	18 (19)	14 (18)
Charlson Comorbidity index at time bDMARD started, median (IQR)	2 (2 – 3)	2 (2 – 3)
Estimated 10-year survival at the time bDMARD started, median (IQR)	90 (77 – 90)	90 (77 – 90)

* age at diagnosis
** dose not known in six females and two males

(n = 61), and most were on etanercept and tocilizumab; 75% remained on the original bDMARD with an adequate compliance (Table 3). Approximately one fifth of patients stopped bDMARD (n = 16), mostly due to infection but also because of primary or secondary failure or deliberately due to subjectively controlled disease activity. One third of pa-tients (n = 22) switched from the original bDMARD, and eight patients required further switches. Up to three and four 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 significant-ly decreased from 74% to 30% (*p* < 0.001, chi square test

Table 2 – Age distribution, professional situation, schooling, marital status and socio-economic status at recall*

Age range (y) (n = 77)	n (%)
27 - 36 y	1 (13)
37 – 46 y	5 (6.5)
47 – 56 y	17 (22.1)
57 – 66 y	26 (33.8)
≥ 67 y	28 (36.3)
Professional situation*	
Employed	21 (27.6)
Unemployed	8 (10.5)
Retired	37 (48.7)
Student	2 (2.6)
Stay at home parent	6 (7.9)
Other	2 (2.6)
Schooling*	
Cannot read or write	1 (1.3)
Can read and write but no schooling	3 (3.9)
First 4 years	31 (40.8)
First 6 years	4 (5.3)
First 9 years	15 (19.7)
Completed schooling (12 years)	9 (11.8)
University degree	13 (17)
Marital status*	
Single	13 (17.1)
Married	43 (56.6)
Divorced	11 (14.5)
Widow	9 (11.8)

* missing information in one patient

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% of patients presented hand deformities, but the median number of deformities per patient was generally low. Dyslipidemia (53%) and arterial hypertension (43%) were equally distributed among the participants but chronic anxiety (18%), smoking (14%) and obesity (10%) were only registered in females. The original age difference between males and females was no longer present, with no other difference between genders concerning 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 men than women, estimating a lower 10-year survival for the former (p = 0.019) (Appendix 1, Table 2; see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13605/Appendix_01.pdf).

At recall, DAS28-ESR and HAQ were significantly lower when compared to the pre-bDMARD values, both with a p value < 0.001 (Wilcoxon Signed Rank test). However, the median DAS28-ESR of 3.2 (IQR 2.390 – 3.950) was borderline between low and moderate disease activity and the median HAQ-DI index was 1.310 (IQR 0.500 – 1.810), indicative of mild to moderate disability. Additionally, at recall, there was no significant difference in DAS28-ESR or HAQ when comparing patients on bDMARD with patients off bDMARDs (p = 0.917 and 0.975, respectively - Mann Whitney-U test). Of note, the pre-bDMARD HAQ could only be obtained for 28 of the 77 patients at recall.

Recall patient cohort: health related quality of life outcomes

Lower scores on the SF-36 reflect poorer HR-QoL, particularly affecting the physical domains, general health perception and vitality in our patient cohort (Fig. 1). 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. Regarding EQ-5D-3L (Table 3), the mean calculated score and VAS were 0.45 (± 0.3) and 60.64 (± 22.1), respectively. There were no significant differences in the EQ-5D-3L domains between men and women (Appendix 1, Table 2; see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13605/Appendix_01.pdf). Moderate yet significant correlations were found between PCS, MCS and EQ-5D-3L mean score and VAS (Appendix 1, Table 3: see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13605/Appendix_01.pdf).

Full data regarding professional status are shown in Appendix 1, Table 4 (see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13605/Appendix_01.pdf). Unemployed patients (n = 7) had a significantly lower EQ-5D Portuguese tariff when compared to employed patients (n = 19) (p = 0.012, T-test), with a similar age; even though not significantly, unemployed patients had higher DA28, HAQ and number of deformities in comparison to the latter.

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 (Table 4). The estimated 10-year survival rate at the time of first biological therapy was significantly different between the deceased patients and the recall group (p = 0.006) with median values of 65 (29 – 77) and 90 (77 - 90), respectively (Appendix 1, Table 5: see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13605/Appendix_01.pdf).

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, with our first patient ongoing regular follow-up since treatment onset. With a median age of 50 years, our patients presented a high disease activity (median DAS28 of 5.30)
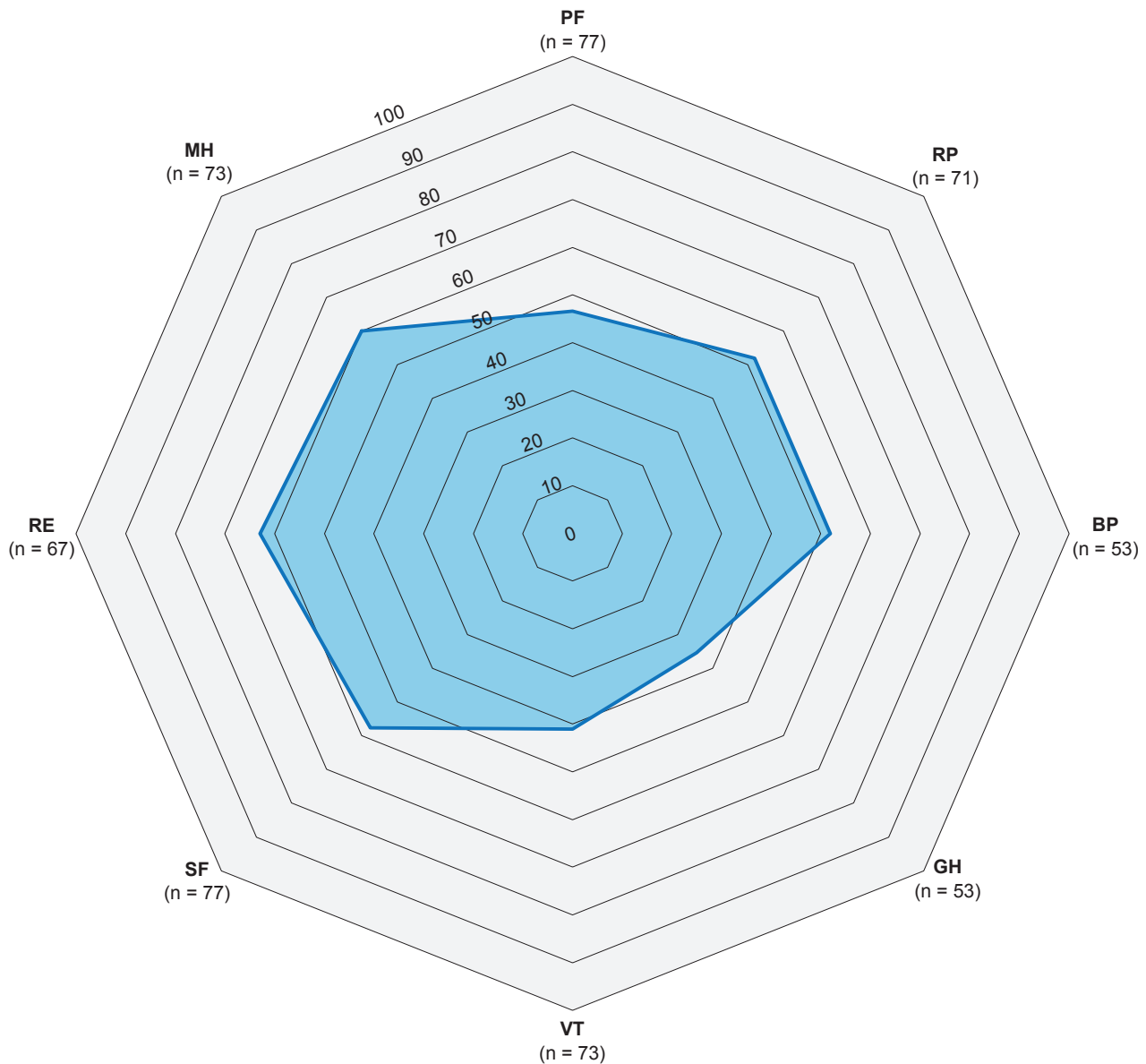
Figure 1 – Health-related quality of life using the SF-36 health survey. Values are shown for each dimension: physical functioning (PF), role limited by physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limited by emotional problems (RE), and mental health (MH).

and a high HAQ disability index (median of 2.00) despite sDMARD therapy, at pre-bDMARD onset. These indices are known to be inter-related and known to predict irreversible damage, physical and work disability and mortality.[22,23]

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. A recent meta-analysis of 36 randomized clinical trials comparing the standard doses of the five anti-TNF inhibitors combined with MTX with MTX monotherapy 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 the selected European 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 four 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 and which might have been prevented through earlier treatment. At recall, 22 of 54 patients presented hand deformities but the

Table 3 – Disease duration, therapy, disease activity, functional status and EQ-5D-3L at recall

Number of patients	77
Disease duration (y) from diagnosis to recall, median (IQR)	12 (7 – 18)
Duration of follow-up from onset of bDMARD to recall, median (IQR)	7 (4 – 9)
Continued bDMARD by recall, n (% of 77)	61 (79)
Last bDMARD:	
Etanercept, n (%)	31 (51)
Adalimumab, n (%)	5 (8)
Tocilizumab, n (%)	15 (25)
Infliximab, n (%)	1 (1,5)
Rituximab, n (%)	6 (10)
Golimumab, n (%)	2 (3)
Abatacept, n (%)	1 (1.5)
Retained original bDMARD, n (%)	46 (75)
Compliance with bDMARD over the past year (n = 56)	45 (80)
Had discontinued bDMARD by recall, n (% of 77)	16 (21)
Reason for discontinuation:	
1. Primary failure to bDMARD, n (%16)	2 (13)
2. Secondary failure to bDMARD, n (%16)	2 (13)
3. Infection, n (% 16)	6 (38)
4. Neoplastic disease, n (% 16)	1 (6)
5. Remission, n (% 16)	3 (19)
6. Other, n (% 16)	2 (13)
Retained original bDMARD, n (% of 61)	46 (75)
Switched bDMARD, n (% of 61)*	22 (36)
1. Once, n (% 22)	14 (64)
2. Twice, n (% 22)	6 (27)
3. Thrice, n (% 22)	1 (5)
4. Fourth, n (% 22)	1 (5)
Compliance with bDMARD over the past year (n = 56)	45 (80)
Methotrexate, n (% of 77)	17 (22)
Methotrexate dose mg/week, median (IQR)	15 (10 – 20)
Steroids, n (% of 77)	23 (30)
Prednisolone equivalent mg/day, median (IQR)	5 (5 – 10)
Steroids plus bDMARD, n (% of 61)	16 (26)
Steroids having discontinued bDMARD, n (% of 16)	7 (43)
Deformities, n (%) – 54 patients evaluated	22 (41)
Deformities/patient, median (IQR)**	0.5 (0 – 2.25)
Recall HAQ, median (IQR) n = 77	1.310 (0.500 – 1.810)
Recall DAS 28 – ESR, median (IQR) n = 72	3.200 (2.390 – 3.950)
- high disease activity (HDA) > 5.1, n (%)	8 (11)
- moderate disease activity (MDA) ≥ 3.2 and ≤ 5.1, n (%)	27 (37)
- low disease activity (LDA) ≥ 2.6 and < 3.2, n (%)	18 (25)
- remission < 2.6, n (%)	19 (26)
EQ-5D 3L (n = 76)	
Mobility, mean (SD)	1.72 (0.51)
Personal care, mean (SD)	1.65 (0.58)
Usual activities, mean (SD)	1.76 (0.59)
Pain and unwell, mean (SD)	1.97 (0.57)
Anxiety and depression, mean (SD)	1.72 (0.72)
EQ-5D 3L Visual Analogue scale (VAS), mean (SD)	60.64 (22.07)
EQ-5D 3L score – Portuguese tariff, mean (SD)	0.45 (0.3)

* 5 patients switched and then stopped
** Missing information in 23 patients

highest number of deformities per patient was 2.25. 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. Even though significantly lower, the HAQ disability index continued to reveal severe functional disabilities.

After a median duration of seven 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. In the latter, a higher frequency of patients (50%) discontinued their first bDMARD mainly due to treatment failure (55%) with a much lower frequency of infections (4%).[29] Of note, in those patients who died, the Charlson co-morbidity index was significantly higher at treatment onset and bDMARD was discontinued more frequently than in the recall group.

Table 4 – Demographic and clinical characterization of deceased patients or lost to follow-up

Characteristics	
Alive but lost to follow-up, n (% of 94)	7 (7)
- Female:Male	5:2
- Went to live abroad, n	4
- Followed at another hospital in Portugal, n	3
- Age (y) bDMARD started, median (IQR)	44 (36 – 54.5)
- Patient age (y) at the time lost to follow-up, median (IQR)	47 (39 – 60)
- Disease duration (y) from time of diagnosis to first bDMARD (median ± IQR)	2 (1 – 4)
- Disease duration (y) at the time lost to follow-up, median (IQR)	4 (3 – 5)
- Either or anti-CCP/RF positive	5
- Anti-CCP and RF negative	2
- Charlson comorbidity index at the time bDMARD started, median (IQR)	1 (1 – 2)
- % Estimated 10 year survival at the time bDMARD started, median (IQR)	96 (86.5 – 96)
- bDMARD:	
- Etanercept, n; later switch to rituximab, n	4; 1
- Tocilizumab, n	1
- Infliximab switched to abatacept, n	1
Death, n (% of 94)	6 (6)
- Female:Male	3:3
- Cause of death unknown	3
- Cause of death known:	
- Pneumocystis pneumonia	1
- Pulmonary tuberculosis	1
- Stroke	1
- Age (y) bDMARD started, median (IQR)	60 (57 – 63)
- Age (y) at time of death, median (IQR)	66 (61 – 67)
- Disease duration (y) from time of diagnosis to first bDMARD (median ± IQR)	7 (3 – 11)
- Disease duration (y) at time of death (median ± IQR)	16 (8 – 21)
- Either or anti-CCP/RF positive, n (%)	7 (100)
- Charlson comorbidity index at time bDMARD started, median (IQR)	3.5 (3 – 4.75)
- % Estimated 10 year survival at time bDMARD started, median (IQR)	65 (29 – 77)
On methotrexate and bDMARD at time of death (n=2):	
- Etanercept, n	1
- Adalimumab, n	1
Off bDMARD at time of death (n=4):	
- Previous etanercept, n	2
- Previous adalimumab, n	1
- Previous rituximab, n	1

When compared with the frequencies of employed Portuguese people (pordata.pt - 2017), of which the majority 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 surprisingly, at recall, almost 50% of our patients were pensioners. The median age of the unemployed patients (57.5 years) was nearing retirement age, but it should be noted that despite bDMARD therapy, 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 score calculated with the Portuguese tariff was 0.45 (± 0.3), effectively placing our RA patients at a low score regarding HR-QoL. Interestingly, baseline mean EQ-5D-3L and HAQ scores for a Greek population of RA patients were 0.57 and 0.75, (our scores being 0.45 and 1.3) respectively. In this respect, higher HR-QoL scores clearly correlated with a lower functional impairment as measured by HAQ.[31] We nevertheless believe that our therapeutic strategies have provided benefit as shown 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 attempt to verify both the efficacy of particular drug regimens or compare them and evaluate how many patients became work-disabled due to disease. As bDMARD therapy was started late in the course of disease, we cannot assess if those who started early had clinical improvement compared with patients with a delayed onset of therapy. Moreover, the dynamic nature of RA therapy cannot be reflected in this cross-sectional design. After recall, some of the patients who had moderate or high disease activity were switched to alternative therapies that proved effective; other patients that were controlled subsequently lost response.

CONCLUSION

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. Most patients retained the original bDMARD, few switches were required and the main 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 reflecting 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.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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