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Starting of biological disease modifying antirheumatic drugs may be postponed in rheumatoid arthritis patients with multimorbidity
Single center real life results

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Abstract

The objective of this study was to assess the frequency of comorbidities and multimorbidities in rheumatoid arthritis (RA) patients under biologic therapy and their effects on biological disease modifying antirheumatic drugs (DMARDs) choice, timing, and response.

Hacettepe University Biologic Registry (HUR-BIO) is single center biological DMARD registry. Cardiovascular, infectious, cancer, and other comorbidities were recorded with face to face interviews. Multimorbidity is defined as >1 comorbidity. Disease duration, initial date of biological DMARDs, initial and overall biological DMARD choice were recorded. Disease activity score-28 (DAS-28) responses were compared to comorbidity presence and multimorbidity.

Total of 998 RA patients were enrolled into the study. The mean age was 53.1 (12.5) and mean disease duration (standard deviation [SD]) was 11.7 (7.5) years. At least 1 comorbidity was detected in 689 (69.1%) patients, 375 (37.9%) patients had multimorbidity. Patients had mean 1.36 ± 1.32 comorbidity. The median durations of first biological DMARDs prescription were 60 (3–552) months after RA diagnosis. For multimorbidity patients, the median first biological prescription duration was longer than the duration for patients without multimorbidity (72 [3–552] vs 60 [3–396] months, $P < .001$). The physicians prescribe tumor necrosis factor inhibitor (TNFi) biological drugs less frequently than other biological DMARDs in patients with at least 1 comorbidity (66.2% vs 74.5%, $P = .007$) or multimorbidity (34.6% vs 43.5%, $P = .006$). Patients with comorbidities and multimorbidity achieved DAS-28 remission less frequently than patients without comorbidity (31.6% vs 42.6%, $P = .012$ and 27.2% vs 39.7%, $P = .001$, respectively).

In real life, physicians may postpone to prescribe biological DMARDs and less frequently choose TNFi biological drugs in patients with multimorbidity. Furthermore, comorbidity may have a negative effect on the treatment response.

Abbreviations: anti-CCP = anti-citrullinated peptide, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, CV = cardiovascular, CVA = cerebrovascular accident, CVEs = cardiovascular events, DAS28-ESR = 28-joint activity calculator-erythrocyte sedimentation rate, DMARDs = disease modifying antirheumatic drugs, ESR = erythrocyte sedimentation rate, HAQ-DI = Health Assessment Questionnaire-Disability Index, HbsAg = Hepatitis B surface antigen, HBV = Hepatitis B (HBV), HCV = Hepatitis C (HCV), HT = hypertension (HT), HUR-BIO = Hacettepe University Biologic Registry, RA = rheumatoid arthritis, RF = rheumatoid factor, SD = standard deviation, T2D = Type 2 diabetes, TB = tuberculosis, TNFi = tumor necrosis factor inhibitor, TST = tuberculin skin test, VAS = visual analog scale.

Keywords: comorbidity, disease modifying antirheumatic drugs (biological), multimorbidity, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, systemic inflammatory disease which mainly affects the synovial membrane of joints but also have extra-articular involvement.[1] Chronic progressive diseases such as RA may cause functional disability. RA patients have increased risk of either morbidity or mortality. At least 60% RA patients have 1 comorbidity, furthermore 29% RA patients have multimorbidities.[2] Although, RA is a burdensome disease for most of the patients, comorbidities usually provide additional disadvantageous contribution to RA course.[3]

It is well known that the importance of comorbidity on disability progression has been emphasized in a large RA cohort, particularly cardiovascular disease and higher overall burden of comorbidities.[4] On the other hand, positive or negative effects of comorbidities on selection of biological disease modifying antirheumatic drugs (DMARDs) in RA patients were not frequently

assessed in the real life biological registries. Comorbidities, for instance chronic infections, may change the biological DMARD choices. For example, physicians may choose other than tumor necrosis factor inhibitor (TNFi) biological drugs with previous tuberculosis history or premalign diseases. Moreover, other comorbidities, for instance type 2 diabetes (T2D) or obesity may force the physicians to choose one class of biological DMARDs than others. One of the multicenter study related with comorbidity in RA demonstrated that multimorbidity can be seen 65.4% of RA patients.[5] However, the effects of chosen treatments on multimorbidity and the response to biological DMARDs were not emphasized so far. Another important point is the surgeries. Surgical history, for example orthopaedic surgeries, may also effect the disease course and treatment options.

The objective of this study was to assess comorbidities and surgical history in the well-designed observational RA cohort under biological DMARDs. Effects of comorbidities, multimorbidity, and surgeries on choice of biological DMARDs choose, timing of biological DMARDs, and response of biological DMARDs were evaluated in this single center biological RA cohort.

2. Methods

2.1. Study population and patient's selection

Hacettepe University Biologic Registry (HUR-BIO) is single center biological registry since 2005.[6–9] RA was defined according to physician's decision. This diagnostic decision is based on type and side of articular involvement, tender and swollen joint counts, rheumatoid factor (RF) and anti-citrullinated peptide (anti-CCP) positivity, symptom duration, radiologic findings, and acute phase reactants. If needed for differential diagnosis; musculoskeletal ultrasonography or magnetic resonance imaging was done. All RA patients with at least 1 biological drug prescribed were consequently recorded in this registry. After 2012, all known comorbidities reported by patients were evaluated by a standard questionnaire. By August 2016, HUR-BIO included 1235 patients with RA and 998 patients were evaluated by a standard questionnaire and assessed for comorbidities. Ethical approval for this study was provided by the Ethical Committee of Hacettepe University Hospitals.

2.2. Data collection and rheumatological assessment

At baseline, age, sex, symptom duration, disease duration, and education level were recorded. Current and past synthetic and biological DMARD usage were noted. Positivity for the RF and anti-CCP results were recorded from medical files. At baseline and every outpatient visit, disease activity was measured with tender joint count (28 joints), swollen joint count (28 joints), and patient's global assessment of disease activity on a visual analog scale (VAS) (0–100 mm), pain (VAS 0–100 mm), fatigue (VAS 0–100 mm), serum C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR). Composite disease activity was calculated by the disease activity score-28 (DAS-28-ESR). DAS28-ESR <2.6 was defined as remission, ≥2.6 to 3.2 as low activity, >3.2 to ≤5.1 as moderate, and >5.1 as high.[10] Functional assessment was evaluated by the Health Assessment Questionnaire-Disability Index (HAQ-DI) tool. HAQ-DI scored from 0 (no disability) to 3 (unable to do).[11]

2.3. Comorbidities

Comorbidities were assessed by face to face interviews and obtained from patients' medical records. Comorbidities were divided into 4 parts such as cardiovascular, chronic infections, cancer, and others.

Cardiovascular (CV) comorbidities were defined as T2D, hypertension (HT), obesity, hyperlipidemia, chronic kidney disease (CKD), and smoking. Obesity was defined as a body mass index >30 kg/m². Dyslipidemia was defined by Adult Treatment Panel III criteria with serum total cholesterol level >240 mg/dL, low-density lipoprotein cholesterol level >160 mg/dL, high-density lipoprotein cholesterol level <40 mg/dL, and a triglyceride level >200 mg/dL.[12] Additionally, patients requiring lipid-lowering drugs were also considered to have dyslipidaemia. T2D was defined according to the American and European Association for Diabetes as a fasting glucose level >126 mg/dL or a random blood glucose level >200 mg/dL.[13] Patients who did not report to have hypertension but measured diastolic blood pressure >90 or systolic blood pressure >140 were also accepted as having hypertension. CKD definition was accepted, irrespective of the cause of kidney disease, based on the presence of either kidney damage or a glomerular filtration rate of <60 mL/min/1.73 m² for >3 months.[14] Patients with current or past smoking habit were defined as "smoking." Smoking packet-year was also recorded.

Assessed chronic infections were hepatitis B (HBV), hepatitis C (HCV), and latent tuberculosis (TB). Chronic hepatitis B was defined as hepatitis B surface antigen (HBsAg) positivity longer than 6 months.[15] Detection of HCV antibody and HCV RNA in patient specimens by the enzyme immunoassay and polymerase chain reaction provides evidence of HCV infection, respectively.[16] A diagnosis of latent TB infection is made if a patient has a positive TB test result and a medical evaluation does not indicate active TB infection.[17] Latent TB infection was assessed by interferon gamma release assay (Quantiferon-TB gold) after 2011. The Mantoux tuberculin skin test (TST) was used before 2011.

In our social security system, fulfillment of ICD-10 cancer codes is mandatory, therefore hematologic and solid malignancy codes were screened with ICD-10 codes. Other comorbidities were thyroid diseases, asthma or chronic obstructive pulmonary disease (COPD), cerebrovascular accident (CVA), amyloidosis, and osteoporosis. Asthma and COPD were expressed together as chronic pulmonary disease based on medical records and evaluation of respiratory function tests in suspected patients. Hypothyroidism, hyperthyroidism, and multinodular goitre were expressed together as thyroid disease based on medical records. Amyloidosis was defined regarding to tissue biopsy. Osteoporosis was defined as a bone density of 2.5 standard deviations (SDs) below that of a young adult measured by dual-energy x-ray absorptiometry at the hip or lumbar vertebra.[18]

2.4. Classification according to comorbidity counts

In addition to RA, patients with at least 1 comorbidities were defined as "comorbidity positive," others were "comorbidity negative." In addition to RA, patients with at least 2 comorbidities were defined as multi-comorbidities.[2,19]

2.5. Surgical history

Information regarding history of any surgery was identified from RA patients. Frequently performed operations were represented as separate, while others were grouped according to the anatomic locations or organ systems.

2.6. Statistical analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL). The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov–Smirnov) to determine whether or not they were normally distributed. Continuous data were described as mean ± SD if they were normally distributed and median (interquartile range, IQR or min–max) if they were not normally distributed. Categorical variables were presented as percentages. Chi-square test was used to compare categorical variables and Mann–Whitney U test was used to compare non-normally distributed continuous variables. P value of <0.05 was considered as significant.

3. Results

3.1. Study population and demographic data

Total of 998 (80% female) RA patients under biological treatments were enrolled in the analysis (Table 1). The mean disease duration (SD) was 11.7 (7.5) years and the mean symptom duration (SD) was 22.2 (47.1) months. Of all enrolled patients, 187 (18.7%) were older than 65 years. A total of 629 (63.0%) patients had less than high school education, 197 (19.8%) of the patients were graduated from university. The initial biological drugs were followed as; etanercept 263 (26.4%), adalimumab 225 (22.5%), abatacept 176 (17.6), rituximab 127 (12.7), infliximab 103 (10.3%), certolizumab 38 (3.8%), golimumab 38 (3.8%), tofacitinib 15 (1.5%), and tociluzumab 13 (1.3%), respectively. In 353 (35%) patients, biological drugs were switched to another biological DMARD. Median biological follow-up period of the RA patients was 37.7 (1.5–211) months.

3.2. Comorbidities
3.2.1. Cardiovascular comorbidities.
The most common CV comorbidities before biological treatment were hyperlipidaemia 448 (44.9%), obesity 447 (44.6%), smoking 399 (40.0%), hypertension 309 (31.1%), T2D 107 (10.8%), CKD 48 (4.8%). Coronary artery disease was found in 56 (5.6%) patients. CVA was found in 4 (0.4%) patients. Smoking habits of patients were as follows, 597 (59.8%) never smoked, 188 (18.8%) current smoker, and 211 (21.2%) ex-smoker. Currently, smoking patients had median 14 (1–80) and ex-smokers had median 12 (0.5–84) packet/y of smoking history.

3.2.2. Chronic infections.
The frequency of infections which were screened before biologic treatment was as below: chronic HBV 23 (2.3%), chronic HCV 16 (1.6%). Fifteen patients (1.5%) had previous HBV infection and 76 (7.6%) had healed HBV infection-naturally immunized.

Latent TB was found in 290 (29%) patients. Quantiferon-TB gold and TST were used 622 and 237 patients, respectively. Quantiferon-TB gold test was positive in 140 (22.5%) patients and TST test was positive 140 (59.1%) patients. Quantiferon-TB gold test was indeterminate in 10 patients. Twenty-two patients received TB prophylaxis due to the appearance of posterior anterior chest x-ray or family history of TB. Twenty-nine (3%) patients in our cohort had tuberculosis history before biologic treatment. Total of 341 (34%) patients received TB prophylaxis.

3.2.3. Cancer.
Fourteen (1.4%) patients had cancer history (10 solid, 4 hematological malignancy) before biological treatments. Patients were followed in median 37.7 (1.5–211) months and 6 solid and 3 hematologic malignancy observed under biological treatments.

3.2.4. Others.
The thyroid disease (13.8%), osteoporosis (10.6%), obstructive pulmonary disease (asthma and/or COPD) (4.8%), and amyloidosis (0.7%) were also observed, respectively.

3.3. Comorbidity counts and related factors

At least 1 comorbidity was detected in 689 (69.1%) patients, moreover 375 (37.9%) patients had multimorbidity. The number

Table 1
Demographic and clinical data of patients.

Parameters	All patients n=998	No comorbidity n=309	≥1 comorbidity n=689	P^*
Age, y, mean±SD	53.1±12.5	46.1±12.4	56.2±11.3	**<.0001**
Female, n (%)	797 (80)	228 (74)	569 (83)	**.01**
Duration of RA "years" n (%)				.057
0 to ≤5	230 (25)	87 (31)	143 (22)	
5 to ≤10	279 (30)	78 (27)	201 (31)	
10 to ≤15	172 (18)	53 (18)	119 (18)	
15 to ≤20	121 (13)	34 (12)	87 (14)	
>20	123 (13)	30 (10)	93 (15)	
Education ≤5 y, n (%)	543 (54.4)	116 (37.5)	427 (62.1)	**<.0001**
RF and/or ACPA, n (%)	609 (61)	181 (58)	428 (63)	.540
Baseline ESR, mm/h, median (min–max)	31 (1–123)	28 (2–123)	35 (1–120)	.090
Baseline CRP, mg/dL, median (min–max)	1.7 (0.05–85)	1.9 (0.05–23.7)	1.6 (0.01–85)	.713
Number of previous DMARDs	2.01±1. 02	1.84±1.09	2.07±0.98	**.05**
Glucocorticoid dose, baseline, median (min–max)	2.5 (0–30)	2.5 (0–30)	2.5 (0–30)	.481
Baseline tender joint counts, median (min–max)	6 (0–28)	6 (0–20)	6 (0–28)	**.024**
Baseline swollen joint counts, median (min–max)	2 (0–20)	2 (0–12)	2 (0–20)	.641
Baseline patient global VAS, median (min–max)	60 (0–100)	60 (10–100)	70 (0–100)	**.004**
Baseline pain VAS, median (min–max)	70 (0–100)	70 (0–100)	70 (0–100)	.087
Baseline fatigue VAS, median (min–max)	70 (0–100)	60 (0–100)	70 (0–100)	.471
Baseline HAQ-DI, median (min–max)	0.95 (0–2.9)	0.77 (0–2.5)	1.0 (0–2.9)	**<.0001**

ACPA = anti-citrullinated protein antibody, CRP = C-reactive protein, DMARDs = disease-modifying antirheumatic drugs, ESR = erythrocyte sedimentation rate, HAQ-DI = The Health assessment questionnaire disability index, RF = rheumatoid factor, SD = standard deviation, VAS = visual analogue scale.
* Patients without comorbidity and patients with at least 1 comorbidity were compared.
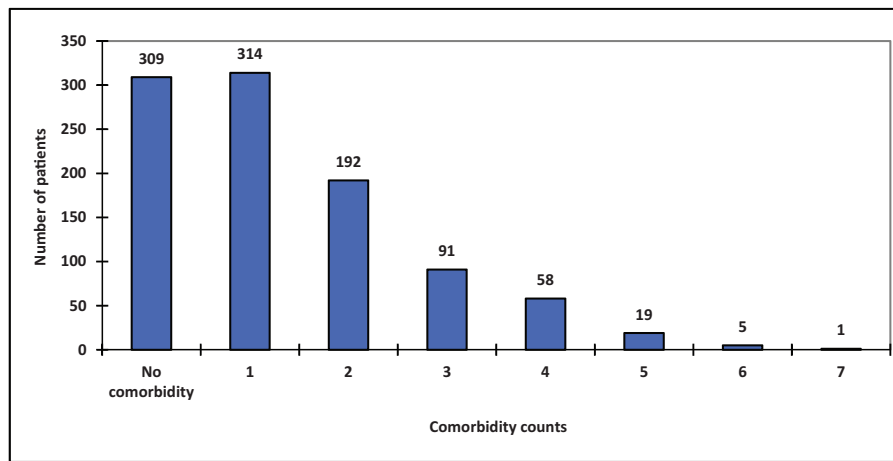Bold numbers show the statistically significant values.

Figure 1. Distribution of comorbidity counts.

of patients with various comorbidities is shown in Fig. 1. Our RA patients had mean 1.36 ± 1.32 comorbidities. Patients who are female (1.43 ± 1.34 vs 1.06 ± 1.20, $P < .001$), who have low education level (1.67 ± 1.40 vs 0.99 ± 1.12, $P < .001$), and some type of surgery knee prosthesis (2.09 ± 1.70 vs 1.31 ± 1.28, $P < .001$), cholecystectomy (2.19 ± 1.35 vs 1.29 ± 1.30, $P < .001$), urinary surgery (2.05 ± 1.58 vs 1.34 ± 1.31, $P = .001$), cardiac surgery (2.29 ± 1.65 vs 1.33 ± 1.30, $P < .001$) had higher comorbidity counts.

In all registry population, first biological drugs were prescribed median 60 (3–552) months after RA diagnosis. For multi-morbidty patients, median first biological prescription duration was longer than without multimorbidty patients (72 [3–552] vs 60 [3–396] months, $P < .001$). According to comorbidity counts, there was no difference for single biological treatment choice. On the other hand, regarding to first biological drugs, physicians less frequently choose TNFi biological drugs over other biological DMARDs in patients with at least 1 comorbidity (66.2% vs 74.5%, $P = .007$) or multimorbidity (34.6% vs 43.5%, $P = .006$). According to DAS-28-ESR response, remission, low, moderate, and high disease activity were achieved in 34.9%, 14.4%, 38.5%, 12.2% patients, respectively. Remission was less frequently achieved in both patients with at least 1 comorbidity or multimorbidity (Fig. 2). Patients with at least 1 comorbidity had more frequently HAQ-DI score >1 (28.8% vs 18.4%, $P = .001$), meanwhile patients with multimorbidity had worse HAQ-DI scores also >1 (34.9% vs 20.0%, $P < .001$) in the last control visits.

3.4. Surgical history

The whole surgical history of patients was shown in Table 2. Total of 626 (63%) patients had at least 1 surgery history. Moreover, 264 (26.5%) patients had history of orthopedic surgery included spinal, extremity, carpal tunnel, and knee/hip prosthesis. Patients with history of orthopedic surgery had worst baseline functional status than without orthopedic surgery (median HAQ score 1 [0–2.9] vs 0.8 [0–2.5], $P = .002$). Patients with knee prosthesis had multimorbidity more frequently (35 [9.3%] vs 27 [4.3%], $P = .002$). However, there were no relation between comorbidity counts and hip prosthesis. Median first biological prescription duration was longer in patient with history of orthopedic surgery than patients without history of orthopedic surgery (90 [3–552] vs 60 [3–408] months, $P < .001$). In the last visits, the percentage of patients with DAS28-ESR remission (26.7% vs 38.0%), low disease activity (13.8% vs14.7%), and HAQ-DI scores ≤ 1 (62.3% vs 78.9%) were significantly low in patients with history of orthopedic surgery.

4. Discussion

In this study comorbidities and surgical histories were investigated on RA patients getting biological treatments. At least 1 comorbidity exists in around 70% of RA patients while ≥ 2 comorbidities were detected in around 40% of the patients. It was found that patients with comorbidities have received biological treatments approximately 1 year later and TNFi group drugs were less preferred among biological treatments.
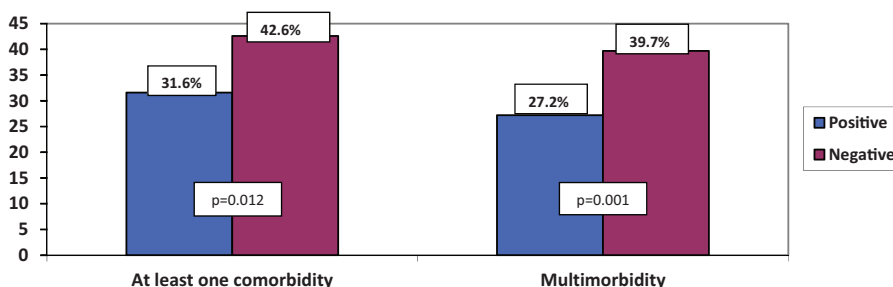

Figure 2. DAS28-ESR remission rates in at least 1 comorbidity and multimorbidity. DAS28-ESR = 28-joint activity calculator-erythrocyte sedimentation rate.

Table 2

Surgery history of the patients.

Surgeries	Total n = 998 n, (%)	Female n = 797 n, (%)	Male n = 201 n, (%)	P
Gynecologic surgery	127 (12.7)	127 (15.9)	–	
Orthopedic extremity surgery	90 (9)	72 (9)	18 (8.9)	.960
Appendectomy	89 (8.9)	79 (9,9)	10 (5.0)	**.027**
Spinal surgery	87 (8.7)	79 (9,9)	8 (4)	**.007**
Cholecystectomy	79 (7.9)	72 (9)	7 (3.5)	**.009**
Cataract	79 (7.9)	64 (8)	15 (7.4)	.780
ENT surgery	77 (7.7)	61 (7.6)	16 (7.9)	.895
Knee prosthesis	63 (6.3)	58 (7.3)	5 (2.5)	.14
Thyroid surgery	60 (6.0)	57 (7.1)	3 (1.5)	**.002**
Hip prosthesis	45 (4.5)	35 (4.4)	10 (5)	.805
GIS surgery	43 (4.3)	31 (3.9)	12 (5.9)	.198
Abdominal hernia repair	40 (4.0)	25 (3.1)	15 (7.4)	**.005**
Urological surgery	36 (3.6)	20 (2.5)	16 (7.9)	**<.0001**
CTS surgery	32 (3.2)	30 (3.8)	2 (1)	**.046**
Breast surgery	16 (1.6)	16 (2)	0 (0)	**.042**
Cardiovascular surgery	31 (3.1)	23 (2.9)	8 (4)	.430
Pulmonary surgery	12 (1.2)	6 (0.8)	6 (3)	**.01**

CTS = carpal tunnel syndrome, ENT = ear, nose, and throat, GIS = gastrointestinal system.
Bold numbers show the statistically significant values.

Two third of our patients have at least 1 surgical history, meanwhile one-fourth have orthopedical surgery past. When comorbidity related factors were examined, an interrelation was detected with female sex, older age, long distance duration, and lower education level and having the comorbidities. The COMORA study, included patients from 17 different nations, showed us the regional differences of characteristics demographics in RA patients.[20] A previous study stated that count of comorbidity lessens while level of education increases.[5] On the other hand, 2 prior studies encounter that more male patients frequently have more comorbidities among RA patients.[2,21] This conclusion is incompatible with our study.

The most important discovery in our study is Rheumatology specialists postponing the decision to start the treatment with existing comorbidities. In literature a lot of factors have been represented that affect the kick-off of biological treatment. For instance, in a study by Yelin et al[22] the rates of starting biological treatments are presented low with the existing comorbidities, low level of income, older than 70 years old patients living alone, and away from central settlements. A study by Radner et al[5] indicates around 10% decrease in the prescription of biological treatments for every further comorbid case on RA patients. However, as far as we know an output hasn't been found that shows a delay in starting of biological treatments on patients. In real life before they decide on biological treatments, practitioners look into underlying chronic infections like tuberculosis, hepatitis B, or conditions that has tendency for the patients to have cancer. They can start biological treatments faster with existing active disease considering the low possibility of side effects on patients who don't have any comorbidity. On a RA patient with comorbidity and multimorbidity, starting a biological DMARD treatment can be delayed with synthetic DMARD alterations, DMARD combinations, or possibly increase of steroid dosage, even though the disease is active. Our results indicate in real life practice these kind of delays are executed. On the other hand, in Mexico and Japan, in 2 separate studies assessing RA treatments point out that biological treatments start earlier on patients who are young and have comorbidities.[23,24] These studies are incompatible with our output. Another important characteristic of our study is to reveal

the tendency of practitioners in selecting first biological DMARDs treatments apart from TNFi therapy in patients with comorbidities. This selection of treatments can be explained by the increase in comorbidities and possible expected side effects. Although there is no consensus on age, infectous risk, and comorbidities that affect the choice of the biological drugs in patients with RA, switching to biological treatments apart from TNFi are also supported for most TNFi insufficient responders.[25,26] Our real life study demonstrated that comorbidties affect the choice of first line biological DMARDs however we couldn't find significant differences in the choice of second line biological DMARDs and swapping to biological treatments apart from TNFi. Furthermore, there was no significant differences between the groups with or without history of orthopedic surgery regarding the choice of first line and second line biological therapy.

Comorbidities also have impact on responses of RA patients to biological DMARD treatments. In our study, although swollen and tender joint counts and acute phase responses are similar, comorbid conditions accompanying RA create additional burden on the patients. The patients with comorbidities have higher patient global assessment than patients without comorbidities. That is why on patients with ≥2 comorbidities, it is harder to obtain DAS-28 remission after biological treatments. This consequence lays emphasis on the necessity to consider the reflection of the other conditions over the patients' overall projection. Similarly, even though disease activity is comparable, the ratings of functional disability and deformity in patients who have comorbidities before and after the treatments are distinct. In addition, orthopedic surgery and knee replacement appear frequently in patients with multimorbidities. It is conceivable that these surgical operations contribute to functional disability. As a result, this condition makes us think that diseases or orthopedic operations in addition to RA damage the quality and functionality of life.

Our biological registry consistently demonstrated that cardiovascular comorbidity and related factors were frequently seen in RA patients. Furthermore, in a study by Ruscitti et al,[27] high values of DAS28 was associated with cardiovascular events (CVEs) and to prevent CVEs, they suggested good control of

disease activity besides controlling traditional risk factors. In another study HT, longer disease duration and exposure to steroids were significant predictors of having T2D in RA patients.[28] Moreover, 1 study conducted in Italy shows that, cardiovascular comorbidities are much more related with disease activity in RA patients than other comorbidities.[29] The close associations between uncontrolled disease activity due to treatment delay or failure and glucose metabolism derangement is thought to be the cause of inefficiency of the treatment.[30] In a study by Crepaldi et al,[29] hyperlipidemia was associated with low disease activity but T2D, ischemic heart disease and obesity were associated with high disease activity. Therefore, types of comorbidity should be taken into account that can also affect the disease course differently.

Duration of disease, longer follow up, concomitant steroid therapy, and comorbidities were associated with infection.[31] Previous studies also reported higher frequency of serious infections in older age patients with biological therapy.[31,32] There should be a balance between the therapy, disease activity, comorbidities, and risk of infection.[31–34] In our study, we could only provide the data of tuberculosis and hepatitis that were routinely screened during the biological therapy. Thus, underreporting of some other infections in our cohort, we couldn't give any information like previous studies about infection in relation between biological drugs, disease activity, and comorbidities.

The competency of our study is substantially to comprise real life data collected from face to face interviews with 998 RA patients taking biological DMARDs whose assessments were concluded. Elderly patients were not isolated from this assessment. However, the study only includes patients using biological DMARDs and cannot be generalized to entire RA patients. In our study, although 15 different comorbid conditions were examined, the fact that psychological conditions like depression and anxiety disorders hasn't been studied is a deficiency. Another flaw is that it includes results from only 1 center. Similar results should be investigated from other biological registries. Also, in this study, the systematic evaluation of RA patients for evidence of comorbidities, may uncover previously undiagnosed conditions in some patients. There may be some bias in our work, as mentioned in previous studies. Comorbidities, which are frequently screened and more associated with the RA can be overestimated, on the other hand comorbidities which can be potentially life-threatening may have been lost from the population before the cohort was established.[20]

Like similar studies, our study also confirms that accompanying diseases are prevalent on patients who start biological treatments. Comorbid conditions have adverse effect on disease activity, functional condition, and response to treatment. This situation may rise from both efficient treatment starting late and response to treatment being less effective than burden of the existing disease. RA assessment tools being affected by comorbid conditions are an issue while evaluating disease activity. Especially, the restrictions of assessment tools in routine practices must be taken into account while evaluating the disease activity on multimorbid patients. Consequently, HUR-BIO real life RA cohort demonstrates that patients with comorbidities are prescribed biological DMARD treatments later and their responses to treatments are worse than patients without comorbidities.

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