

Article

Is There a Symmetry in Disease Control and Quality of Life of Patients with Rheumatoid Arthritis Treated with Biological Therapy?

Konstantin Tachkov ¹ , Vladimira Boyadzhieva ², Nikolay Stoilov ², Konstantin Mitov ¹ and Guenka Petrova ^{1,*} 
¹ Faculty of Pharmacy, Medical University of Sofia, Sofia 1000, Bulgaria; tachkov@outlook.com (K.T.); kmitov@pharmfac.mu-sofia.bg (K.M.)

² Faculty of Medicines, Medical University of Sofia—University Hospital “St. Wan Rilska”, Sofia 1612, Bulgaria; v.boyadzhieva@medfac.mu-sofia.bg (V.B.); nstoilov@medfac.mu-sofia.bg (N.S.)

* Correspondence: gpetrova@pharmfac.mu-sofia.bg; Tel.: +359-292-365-45

Abstract: This study aims to analyze and compare the disease activity control and quality of life of patients with rheumatoid arthritis (RA) who were treated with biological products in real-life settings. We tried to determine whether there is a symmetry in the performance of the biological molecules between each other and with the first Janus kinase (JAK) inhibitor. This is an observational, longitudinal, real-life study performed in the biggest rheumatology clinic during the period 2012–2020 comparing quality of life, cost of therapy, and disease control via different clinical measures. In all three disease activities measurement instruments, we observed an improvement for all biologic and target synthetic medicines. The disease activity score (DAS28) score decreased from 5.06 to 3.01, on average, for all INNs, suggesting that the majority of patients move away from moderate to low disease activity. The clinical disease activity index (CDAI) score decreased from 25.9 to 9.4, also indicating that patients with moderate disease activity reached a low level of activity. Similar results are reflected in the score, which fell from 27.7 to 10.3, again confirming the improvement to a low level of disease activity for patients treated with all INNs. Logically, with the successful control of disease activity, the quality of life (QoL) of the observed patients improved from 0.77 to 0.83 after a one-year follow up, as measured with the EuroQuol 5D-3L (EQ5D). Based on these results, we can consider that the observed biological INNs perform symmetrically in terms of the control of disease activity and improvement in the QoL of the observed patients. Biological therapy improves the disease control and quality of life of suitable patients with RA in real-life settings. All available biological therapies could be used interchangeably.

Keywords: biological therapy; rheumatology; quality of life; symmetry in clinical response; disease control



Citation: Tachkov, K.; Boyadzhieva, V.; Stoilov, N.; Mitov, K.; Petrova, G. Is There a Symmetry in Disease Control and Quality of Life of Patients with Rheumatoid Arthritis Treated with Biological Therapy? *Symmetry* **2021**, *13*, 538. <https://doi.org/10.3390/sym13040538>

Academic Editor:
Abhijit Chakraborty

Received: 13 March 2021
Accepted: 23 March 2021
Published: 25 March 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Biological therapy is recommended as a second-line therapy for patients with rheumatoid arthritis (RA) when multiple disease-modifying anti-rheumatic drugs (DMARDs) and methotrexate (MTX) cannot sufficiently control disease progression [1]. During the last 20 years, many biological molecules have been included in the RA armamentarium. Infliximab was developed in 1998 as the first monoclonal antibody to human necrosis factor alpha (TNF α) for treating RA [2]. Later adalimumab, etanercept, rituximab, golimumab, and certolizumab were authorized for sale on the market [3]. These chimeric antibodies bind with a high affinity to both soluble and trans-membrane TNF and can reduce synovial inflammation, cartilage degradation, and bone resorption. Despite their specificity, these molecules have demonstrated differential clinical efficacy in studies of RA [4]. There is evidence that patients who do not respond to one antagonist often respond to another [5,6]. These differences are mostly related to the pharmacodynamics, pharmacokinetics, and mechanisms of action, as well as disease heterogeneity. With the advancement

of knowledge regarding RA and intracellular signaling pathways such as Janus kinase (JAK) pathways, new therapeutic agents have been added, such as tofacitinib, an oral JAK inhibitor for the treatment of RA [7]. Tofacitinib is a targeted small molecule which modulates cytokines critical to the progression of immune and inflammatory responses.

Systematic reviews and meta-analyses comparing randomized, controlled trials of biological TNF α inhibitors prove that they are effective treatments compared with a placebo and improve the control of symptoms; improve physical function; and slow radiographically detected, structural changes in the joints of RA patients who are not well controlled by conventional DMARDs [8].

Disease activity may be assessed by employing single instruments or composite scores [9]. The disease activity score (DAS28) is a measure of disease activity based on 28 joints that are examined in this assessment. In most European countries, a score for DAS28 of equal or greater than 5.1 is one of the mandatory criteria required to be eligible for publicly funded treatment with biologic or targeted synthetic (including anti-tumor necrosis factor and JAK inhibitor) therapies [10]. The clinical disease activity index (CDAI) determines the severity of rheumatoid arthritis using only clinical data. A CDAI reduction of 6.5 represents a moderate improvement [11]. The Simplified Disease Activity Index (SDAI) can range between 0 and 100 (roughly, depending on the maximum reasonably assumable C-reactive protein (CRP) level in RA). The response to therapy is considered minor ($\geq 50\%$ reduction), moderate ($\geq 70\%$ reduction), or major ($\geq 85\%$ reduction) when measured with CDAI or SDAI. Moreover, SDAI and CDAI remission states have also been shown to best reflect the reduction in cardiovascular risk and quality of life [12,13]. The quality of life and working capacity are close to normal in CDAI remission [14] as well.

Little is known about the effectiveness of biological molecules for RA therapy in real-life settings [15], with articles focusing more on the second-best approaches tailored to controlling the disease [16]. Our interest was provoked by this gap in the knowledge base, and we set out to make such a comparison.

This study aims to analyze and compare the disease activity, control, and quality of life of patients with RA who were treated with biological products in real-life settings.

We tried to determine whether there is a symmetry in the performance of the biological molecules in between each other and with the first JAK inhibitor.

2. Materials and Methods

2.1. Design of the Study

This is an observational, longitudinal, real-life study performed in the biggest rheumatology clinic at the University hospital “St. Ivan Rilski” in Sofia, Bulgaria, during the period 2012–2020. The study protocol was approved by the ethics committee of the institution. All the participants signed informed consent in accordance with the Declaration of Helsinki. A total of 174 patients who were naïve to biological therapy were consecutively enrolled in the study and followed for a one-year period by rheumatologists. A minimum number of 20 patients in each group was determined to be necessary in order to achieve statistical significance in the groups and, at the same time, to observe the time interval of the study. The initial number of patients selected for this study was 197, but due to lack of efficacy, adverse events, and deterioration, 23 patients were switched to another biological or targeted synthetic DMARD and excluded from the analysis.

The criteria for inclusion were clinically proven RA according to ACR (1987) and/or ACR/EULAR (2010) criteria, previous therapy with DMARDs and/or methotrexate, suitable for therapy with biological medicines or JAK inhibitors. Exclusion criteria were cardiac insufficiency (NYHA III and IV grade), malignant hypertension, infectious diseases, any neoplasms, or proliferative lymph diseases within the previous 5 years.

Rheumatologists' choice of biological therapy was determined by their clinical opinion and not influenced by any other means. Information about the patients' demographic characteristics, gender, age, length of the disease, disease control, quality of life, prescribed medicines, and cost of pharmacotherapy was collected during the observational period. Pa-

tients were treated with 7 INNs of biologicals (certolizumab pegol, golimumab, tocilizumab, etanercept, adalimumab, rituximab, infliximab) and 1 JAK inhibitor (tofacitinib).

The disease control was assessed by the changes in the DAS28-CRP, CDAI, and SDAI, which were measured at the initiation of biological therapy and after 6 and 12 months of follow-up. For a more accurate assessment, we used DAS-28 based on C-reactive protein (DAS28-CRP) in our study. Changes in the quality of life (QoL) were measured with the unidimensional instrument EuroQuol 5D-3L (EQ5D) again at the beginning and after 6 and 12 months of biological therapy. EQ5D provides an aggregated score between 0 (death) and 1 (perfect health) by measuring physical activity, self-care, usual activities, pain, and anxiety. Both instruments rely on patients' self-reported measures.

Changes in the disease control and QoL were compared between the patients assigned to different biological therapies.

2.2. Statistical Analysis

Several statistical methods were employed in this analysis. Descriptive statistics for the changes in the disease activity and QoL scores were performed. T-tests and Kruskal–Wallis tests were applied for variables with normal or non-normal distributions. To explore the probable connection between the observed variables, we performed linear regression and linear correlation (Pearson type) analyses. All the analyses were performed with MedCalc v. 19.2.

3. Results

3.1. Overall Data Analysis

Table 1 presents the characteristics of the observed patients on different biological therapies. The number of patients assigned to different biological INNs varied between $n = 20$ and $n = 30$. The average age was between 52.3 (SD 9.13) and 57.15 (SD 9.05) years, and the average length of the disease was between 6.4 (SD 2.92) and 12.8 (SD 7.56) years.

The average per patient cost of therapy is lower with infliximab, which was the first authorized for sale biological therapy available with two biosimilars in the period, and rituximab due to dosage regimen. Lastly developed were golimumab and tocilizumab with high cost of therapy per patient. In clinical trials, golimumab did not achieve higher effectiveness than infliximab, which would justify such a high cost. [17] However, some authors consider that golimumab has a convenient dosage scheme and facilitated way of administration [18].

In all three disease activities measurement instruments, we observed an improvement for all biologic and target synthetic medicines. The DAS28 score decreased from 5.06 to 3.01 on average for all INNs, pointing out that the majority of patients move away from moderate-to-low disease activity. The CDAI score decreased from 25.9 to 9.4, also indicating that patients with moderate disease activity reach the level of low activity. Similar results are reflected in the score, which fell from 27.7 to 10.3, again confirming the improvement to low level of disease activity for patients treated with all INNs.

Logically, with the successful control of disease activity, the QoL of the observed patients improved from 0.77 to 0.83 after a one-year follow up, as measured with EQ5D.

Based on these results, we can consider that the observed INNs perform symmetrically in terms of the control of the disease activity and improvement in the QoL of the observed patients.

Table 1. Characteristics of the observed patients for each INN.

Characteristic (SD)	Cetrolizumab	Golimumab	Tocilizumab	Etanercept	Adalimumab	Rituximab	Infliximab	Tofacitinib
Number	20	22	30	20	20	20	20	20
Female	19	20	29	16	17	17	15	16
Male	1	2	1	4	3	3	5	4
Average age	55 (10.05)	53.7 (10.16)	55.1 (10.60)	56.15 (9.42)	53.2 (12.92)	57.15 (9.05)	52.3 (9.13)	56.75 (12)
Average length of the disease	9.3 (3.59)	10.82 (6.86)	14.13 (8.38)	11.5 (5.8)	12.8 (7.56)	9.45(5.88)	6.4 (2.92)	7.1 (3.03)
Average total cost of therapy (SD)	2048.53 (708.51)	2688.88 (639.75)	2585.33 (732.78)	1871.80 (681.14)	2493.76 (378.07)	570.74 (654.64)	537.56 (0.004)	1798,25 (0.0004)
DAS28 1st measurement	5.05 (0.43)	5.29 (0.67)	4.83 (0.64)	4.98 (0.58)	5.14 (0.84)	5.19(0.59)	5.26 (0.51)	4.77 (0.77)
DAS28 2nd measurement	3.75 (0.56)	4.69 (2.36)	3.47 (0.71)	3.55 (0.41)	3.57 (0.59)	3.67 (0.44)	4.07 (0.61)	3.46 (0.71)
DAS28 3rd measurement	3.07 (0.44)	2.49 (0.57)	3.07 (0.57)	2.85 (0.45)	3.15 (0.57)	2.95 (0.44)	3.48 (0.73)	3.04 (0.57)
CDAI 1st measurement	25.04 (3.57)	27.63 (6.51)	22.65 (5.27)	24.31 (5.06)	26.71 (6.70)	25.14 (3.56)	25.36 (3.77)	23.83 (4.73)
CDAI 2nd measurement	13.85 (3.56)	13.42 (3.41)	14.19 (4.24)	12.38 (3.42)	13.56 (4.81)	13.31 (3.38)	17.57(3.74)	13.23 (5.9)
CDAI 3rd measurement	9.55 (2.82)	6.78 (3.39)	9.80 (4.08)	7.97 (2.99)	10.05 (4.16)	8.19 (2.35)	12.92 (4.83)	9.96 (3.26)
SDAI 1st measurement	27.22 (4.32)	31.21 (7.74)	25.96 (6.07)	27.7 (5.51)	29.94 (8.23)	27.86 (4.95)	26.6 (3.9)	25.09 (5.11)
SDAI 2nd measurement	15.09 (3.58)	14.73 (4.15)	15.37 (4.64)	13.82 (3.81)	14.81 (5.11)	14.51 (3.83)	18.63 (3.9)	13.98 (6.34)
SDAI 3rd measurement	10.43 (3.12)	7.79 (3.75)	10.45 (4.28)	9.03 (3.11)	10.50 (4.33)	8.93 (2.54)	13.83 (5.06)	11.04 (3.72)
EQ5D 1st measurement	0.757 (0.02)	0.772 (0.04)	0.776 (0.05)	0.779 (0.04)	0.769 (0.03)	0.776 (0.04)	0.765 (0.03)	0.772 (0.04)
EQ5D 2nd measurement	0.780 (0.04)	0.805 (0.05)	0.813 (0.07)	0.820 (0.06)	0.798 (0.05)	0.823 (0.06)	0.806 (0.05)	0.809 (0.06)
EQ5D 3rd measurement	0.796 (0.05)	0.838 (0.06)	0.825 (0.08)	0.837 (0.06)	0.806 (0.06)	0.835 (0.06)	0.832 (0.06)	0.832 (0.06)

3.2. Results from the Statistical Analysis

Table 2 presents the main results of the descriptive statistical analysis. For all disease control measures (DAS28-CRP, CDAI, SDAI), there is a normal distribution of the effects of the therapies for all observed patients for all INNs ($p > 0.05$). The EQ5D scores are not normally distributed. All the p -values of normal distribution hypothesis testing are less than 0.05, meaning that the effect of different therapies of different INNs is not normally distributed among the patients. There is also a statistically significant difference between the scores of all the measured disease control indicators and QoL after the first and third measurements ($p < 0.0001$ to $p < 0.00183$). This means that the improvements in disease control and QoL for patients treated with every biologic and tofacitinib are significant.

Table 3 presents the results of the linear correlation analysis. There are significant correlation coefficients between all INNs and effectiveness varying from 0.991 to 0.999. These results show that the effects of all biologics and tofacitinib strongly influence disease activity and QoL measures—hence the high correlation coefficient. This lends credence to the notion of interchangeability between products, which was also the medical logic behind their development. Every new INN is developed to increase the effect of the already-existing previous INN in the line and to decrease the probability of adverse events. In addition, the regression analysis supports such a conclusion because it is described with linear equation that explains 97.6% of all variations between the different INNs ($p < 0.0001$).

Additional linear correlation analysis (Pearson coefficient) was performed to test the relationships between the three analyzed measures of disease control, QoL, and the cost of therapy (Table 4). A statistically significant correlation was discovered between the QoL and diseases control indicators (DAS28-CRP, CDAI, SDAI), as well as a moderate, statistically non-significant correlation between the cost of therapy and changes in all indicators.

Non-parametric Kruskal–Wallis analysis shows that the most effective therapy is that with golimumab, followed by that with rituximab and etanercept according to DAS28-CRP (Table 5). The median effect of golimumab is 2.745 higher than that of the other biologics and tofacitinib as target synthetic DMARDS. The same is the ranking of INNs according to CDAI and SDAI. In contrast, the changes in the average QoL were not statistically significant.

Table 2. Descriptive statistics.

TEffect_DAS28								
Therapy	adalimumab	Cetrolizumab	etanercept	golimumab	Infliximab	rituximab	tocilizumab	tofacitinib
<i>n</i>	20	20	20	22	20	20	30	20
Minimum	0.240	0.260	0.640	0.470	−0.230	1.000	0.410	0.560
Maximum	3.710	2.820	3.710	4.720	3.080	3.000	4.240	2.760
Mean	1.982	1.975	2.123	2.806	1.775	2.243	1.756	1.735
95% CI	1.565 to 2.398	1.686 to 2.263	1.758 to 2.488	2.318 to 3.295	1.373 to 2.177	1.946 to 2.540	1.422 to 2.091	1.395 to 2.076
25–75 P	1.375 to 2.665	1.635 to 2.375	1.525 to 2.780	1.870 to 3.740	1.275 to 2.395	1.830 to 2.815	1.280 to 2.260	1.050 to 2.405
Normal D.	0.9771	0.1024	0.9938	0.8440	0.5321	0.1198	0.0989	0.1478
TEffect_CDAI								
Therapy	adalimumab	Cetrolizumab	etanercept	golimumab	Infliximab	rituximab	tocilizumab	Tofacitinib
Minimum	5.100	2.000	6.000	−1.200	3.700	10.100	0.300	6.200
Maximum	30.000	27.400	30.000	47.500	19.000	24.200	27.500	23.200
Mean	16.660	15.490	16.334	20.845	12.445	16.951	12.847	13.870
95% CI	13.057 to 20.263	12.751 to 18.229	13.568 to 19.100	16.194 to 25.497	10.554 to 14.336	15.173 to 18.729	10.326 to 15.368	11.439 to 16.301
25–75 P	11.000 to 22.500	12.950 to 19.350	11.750 to 19.500	14.000 to 25.000	10.000 to 16.100	14.700 to 19.000	8.700 to 17.000	8.950 to 17.800
Normal D.	0.1652	0.5968	0.8230	0.4572	0.7471	0.7111	0.7313	0.4161
TEffect_SDAI								
Therapy	adalimumab	Cetrolizumab	etanercept	golimumab	Infliximab	rituximab	tocilizumab	tofacitinib
Minimum	5.120	2.300	6.200	−1.400	3.500	10.700	1,900	6.400
Maximum	33.400	30.700	32.900	56>700	20.000	37.000	29.200	23.200
Mean	19.436	16.790	18.675	23.412	12.775	18.938	15.512	14.057
95% CI	15.556 to 23.316	13.633 to 19.947	15.353 to 21.997	18.005 to 28.819	10.780 to 14.770	16.044 to 21.832	12.601 to 18.423	11.473 to 16.640
25–75 P	12.350 to 25.600	13.200 to 22.200	13.450 to 21.850	16.100 to 30.200	10.500 to 15.250	15.100 to 21.800	9.920 to 21.300	9.000 to 19.430
Normal D.	0.5866	0.9591	0.5515	0.4801	0.7797	0.0211	0.3428	0.0766

Table 2. Cont.

TEffect_EQ5D								
Therapy	adalimumab	Cetrolizumab	Etanercept	golimumab	Infliximab	rituximab	tocilizumab	tofacitinib
Minimum	−0.112	−0.154	−0.245	−0.245	−0.155	−0.154	−0.245	−0.244
Maximum	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Mean	−0.0370	−0.0386	−0.0574	−0.0662	−0.0670	−0.0589	−0.0492	−0.0607
95% CI	−0.0571 to −0.0168	−0.0592 to −0.0180	−0.0898 to −0.0250	−0.0956 to −0.0368	−0.0910 to −0.0429	−0.0825 to −0.0352	−0.0725 to −0.0259	−0.0922 to −0.0291
25–75 P	−0.0815 to 0.000	−0.0730 to 0.000	−0.0900 to 0.000	−0.0950 to 0.000	−0.0950 to −0.0220	−0.0900 to −0.0110	−0.0900 to 0.000	−0.0950 to 0.000
Normal D.	0.0002	0.0015	0.0015	0.0065	0.0296	0.0090	<0.0001	0.0033

Table 3. Results from the correlation analysis of the effect of different INNs.

		Adalimumab	Cetrolizumab	Golimumab	Tocilizumab	Etanercept	Rituximab	Infliximab	Tofacitinib
adalimumab	Correlation coefficient Significance Level P n		0.998 <0.0001 12	0.991 <0.0001 12	0.994 <0.0001 12	0.999 <0.0001 12	0.998 <0.0001 12	0.974 <0.0001 12	0.996 <0.0001 12
cetrolizumab	Correlation coefficient Significance Level P n	0.998<0.0001 12		0.988 <0.0001 12	0.998 <0.0001 12	0.997 <0.0001 12	0.998 <0.0001 12	0.984 <0.0001 12	0.998 <0.0001 12
golimumab	Correlation coefficient Significance Level P n	0.991 <0.0001 12	0.988 <0.0001 12		0.979 <0.0001 12	0.996 <0.0001 12	0.996 <0.0001 12	0.948 <0.0001 12	0.979 <0.0001 12
tocilizumab	Correlation coefficient Significance Level P n	0.994 <0.0001 12	0.998 <0.0001 12	0.979 <0.0001 12		0.992 <0.0001 12	0.993 <0.0001 12	0.991 <0.0001 12	0.997 <0.0001 12

Table 3. Cont.

		Adalimumab	Cetrolizumab	Golimumab	Tocilizumab	Etanercept	Rituximab	Infliximab	Tofacitinib
etanercept	Correlation coefficient	0.999	0.997	0.996	0.992		1.000	0.968	0.992
	Significance Level P	<0.0001	<0.0001	<0.0001	<0.0001		<0.0001	<0.0001	<0.0001
	n	12	12	12	12		12	12	12
rituximab	Correlation coefficient	0.998	0.998	0.996	0.993	1.000		0.972	0.993
	Significance Level P	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001		<0.0001	<0.0001
	n	12	12	12	12	12		12	12
infliximab	Correlation coefficient	0.974	0.984	0.948	0.991	0.968	0.972		0.989
	Significance Level P	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001		<0.000112
	n	12	12	12	12	12	12		
tofacitinib	Correlation coefficient	0.996	0.998	0.979	0.997	0.992	0.993	0.989	
	Significance Level P	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
	n	12	12	12	12	12	12	12	

Table 4. Results from the correlation analysis between the cost of therapy, disease control, and QoL.

Average_total_cost_of_therapy__SD_	Correlation coefficient	−0.419	−0.501	−0.313	−0.446
	Significance Level P	0.3012	0.2055	0.4501	0.2677
	n	8	8	8	8
CDAI_3rd_measurement	Correlation coefficient	−0.419	0.960	−0.256	0.993
	Significance Level P	0.3012	0.0002	0.5414	<0.0001
	n	8	8	8	8

Table 4. Cont.

DAS28_3rd_measurement	Correlation coefficient	−0.501	0.960		−0.332	0.937
	Significance Level P	0.2055	0.0002		0.4213	0.0006
	<i>n</i>	8	8		8	8
EQ5D_3rd_measurement	Correlation coefficient	−0.313	−0.256	−0.332		−0.198
	Significance Level P	0.4501	0.5414	0.4213		0.6381
	<i>n</i>	8	8	8		8
SDAI_3rd_measurement	Correlation coefficient	−0.446	0.993	0.937	−0.198	
	Significance Level P	0.2677	<0.0001	0.0006	0.6381	
	<i>n</i>	8	8	8	8	

Table 5. Dispersion Kruskal–Wallis analysis for the disease control and QoL indicators.

DAS28	N	Average Rank	Different ($p < 0.05$)
(1) ADALIMUMAB	20	85.10	(4)
(2) CETROLIZUMAB	20	84.37	(4)
(3) ETANERCEPT	20	91.15	(4)
(4) GOLIMUMAB	22	121.02	(1)(2)(3)(5)(7)(8)
(5) INFLIXIMAB	20	75.15	(4)
(6) RITUXIMAB	20	102.67	(7)(8)
(7) TOCILIZUMAB	30	67.93	(4)(6)
(8) TOFACITINIB	20	70.42	(4)(6)
CDAI			
(1) ADALIMUMAB	20	90.45	
(2) CETROLIZUMAB	20	90.72	
(3) ETANERCEPT	20	93.15	(5)
(4) GOLIMUMAB	22	117.64	(5)(7)(8)
(5) INFLIXIMAB	20	61.98	(3)(4)(6)
(6) RITUXIMAB	20	102.67	(5)(7)
(7) TOCILIZUMAB	30	66.53	(4)(6)
(8) TOFACITINIB	20	75.72	(4)
SDAI			
(1) ADALIMUMAB	20	99.03	(5)(8)
(2) CETROLIZUMAB	20	86.10	(4)(5)
(3) ETANERCEPT	20	95.95	(5)(8)
(4) GOLIMUMAB	22	115.84	(2)(5)(7)(8)
(5) INFLIXIMAB	20	55.00	(1)(2)(3)(4)(6)
(6) RITUXIMAB	20	98.45	(5)(8)
(7) TOCILIZUMAB	30	77.50	(4)
(8) TOFACITINIB	20	65.70	(1)(3)(4)(6)
EQ5D			
(1) ADALIMUMAB	20	101.47	
(2) CETROLIZUMAB	20	96.78	
(3) ETANERCEPT	20	87.82	
(4) GOLIMUMAB	22	78.20	
(5) INFLIXIMAB	20	73.95	
(6) RITUXIMAB	20	79.00	
(7) TOCILIZUMAB	30	90.60	
(8) TOFACITINIB	20	82.95	

4. Discussion

New therapeutic alternatives that have emerged in the recent years have changed the standards and recommendations for the treatment of RA. With the advent of biologic therapy in routine clinical practice, the use of tumor necrosis factor (TNF) blockers, other biologics like tocilizumab, abatacept, rituximab, and target synthetic DMARDs, such as tofacitinib, have significantly improved quality of life and reduced patient disability [19,20].

Our analysis confirms the effectiveness of biological therapy for patients with rheumatoid arthritis in a real-life setting [20,21]. In contrast with the previous study, this one also included the effect of the first JAK inhibitor, which revealed reduction of disease activity during the year of follow-up. We found it as a reason to accept the importance of the non-inferior effect of tofacitinib as an important amendment in the treatment landscape of Rheumatoid arthritis. All explored disease activity indicators in this study, namely DAS28-CRP, CDAI, and SDAI, showed improved control over the disease [22]. The changes in disease activity are statistically significant and clinically significant. The results obtained by us confirm the principles proposed by EULAR in its recommendations for management of rheumatoid arthritis, updated in 2019. According to them, if the treatment target (remission or minimal disease activity) is not achieved with conventional synthetic DMARD and poor prognostic factors are present, then a biological or tofacitinib should be added to patient therapy [1]. The real-life data from our study prove that both patients on biological treatment and those on targeted synthetic therapy reach minimal disease activity/remission and improvement in quality of life after one year of follow-up. This gives us reason to assume that both groups of DMARDS are possible first-line choices after insufficient effectiveness of conventional synthetic DMARDS. Moreover, the fact that patients responded to therapy positively validates the important place biologics have in the treatment landscape. Although not statistically significant for all INNs, the QoL improved during the one-year follow-up period.

Other meta-analyses provide comprehensive data for efficacy evaluation. Vieira et al. presents data which confirmed that tofacitinib 10 mg/daily combined with Methotrexate was similar in terms of the relative risk (RR) and ACR20/50/70 responses to golimumab, tocilizumab, rituximab, and abatacept in combination with conventional DMARDS during the follow-up of 12 and 24 weeks. [21,22] The results assessing QoL suggests that tofacitinib 10 mg/daily is more effective than placebo and comparable to bDMARDS, measured by HAQ-DI. [21] Other studies present the expert opinion for tailoring the biologic therapy for patients in real-world conditions [23]. The authors consider that the evidence coming from real life setting provides suggestions for the use of biologic drugs and achieving a predictable better outcome, so as to ideally profile the patient to the best of the current knowledge.

In accordance with EULAR recommendations and data from meta-analyses, the National Health Insurance Fund (NHIF) in Bulgaria has adopted requirements for initiating biologic or target synthetic DMARD. Patients must be non-responders to conventional synthetic DMARDS at optimal doses for six months. They also should have failed at least two DMARDS therapy, and one must be Methotrexate 20 mg/weekly. The other DMARDS are one of the following—Leflunomide 20 mg/daily, Resochine 250 mg/daily or Salazopirine 3 g/daily). The disease activity score (DAS28, ESR, or CRP) have to be more than 5.1. The exclusion criteria of the NHIF are the same as in our study.

The current criteria and results from our study allow rheumatologists in Bulgaria to start treatment with a JAK-inhibitor or biologic DMARD based on personal experience and contraindications to DMARD [22]. This allowed a prospective longitudinal study to be conducted in its current form, which included all biologic and tofacitinib available on the market until 2019. This also could explain the relatively close number of patients assigned to different INNs because physicians have to carefully follow the instructions and can choose only from the available at-the-moment products [24].

Our study gives additional information and shows that golimumab is the alternative with high effectiveness over disease control. All available biologicals could be used interchangeably, but golimumab is the alternative with a higher effectiveness over disease control. We do not explore the cost-effectiveness of the alternatives as in the previous study, but, having in mind that the cost of therapy with rituximab is one of the lowest and it is the second most effective alternative, we can assume that this is probably a cost-effective alternative.

We also prove that the TNF α inhibitors could be used interchangeably because of the high correlation between their therapeutic results. This conclusion is supported by a variety of clinical trials and meta-analyses comparing the effect of INNs [25,26]. Therefore, we can consider that there is a symmetry between the therapeutic effect of the analyzed TNF α inhibitors.

5. Conclusions

Biological therapy improves the disease control and quality of life of suitable patients with RA in a real-life setting. All available biological therapies could be used interchangeably.

Author Contributions: Conceptualization, V.B. and G.P.; methodology, K.T., V.B., N.S., and K.M.; software, K.T. and K.M.; validation, V.B. and N.S.; formal analysis, G.P. and V.B.; investigation, V.B. and N.S.; resources, V.B. and N.S.; data curation, K.T. and K.M.; writing—original draft preparation, K.T., G.P., and V.B.; writing—review and editing, K.T.; visualization, K.T. and K.M.; supervision, G.P.; project administration, V.B. and N.S.; funding acquisition, N.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Ministry of Education Fund “Young scientists and postdoctoral fellows”.

Data Availability Statement: Data are available upon request from the authors.

Acknowledgments: The authors acknowledge the staff of the Rheumatology Clinic at the University Hospital “St. Ivan Rilski”, Sofia.

Conflicts of Interest: The authors declare no conflict of interest.

References

- Smolen, J.S.; Landewé, R.B.M.; Bijlsma, J.W.J.; Burmester, G.R.; Dougados, M.; Kerschbaumer, A.; McInnes, I.B.; Sepriano, A.; van Vollenhoven, R.F.; de Wit, M.; et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann. Rheum. Dis* **2020**, *79*, 685–699. [CrossRef] [PubMed]
- Maini, S.R. Infliximab treatment of rheumatoid arthritis. *Rheum. Dis. Clin. N. Am.* **2004**, *30*, 329–347. [CrossRef] [PubMed]
- Tracey, D.; Klareskog, L.; Sasso, E.H.; Salfeld, J.G.; Tak, P.P. Tumor necrosis factor antagonist mechanisms of action: A comprehensive review. *Pharmacol. Ther.* **2008**, *117*, 244–279. [CrossRef] [PubMed]
- Haraoui, B. Differentiating the efficacy of tumor necrosis factor inhibitors. *J. Rheumatol.* **2005**, *74*, 3–7. [CrossRef] [PubMed]
- Bathon, J.M.; Martin, R.W.; Fleischmann, R.M.; Tesser, J.R.; Schiff, M.H.; Keystone, E.C.; Genovese, M.C.; Wasko, M.C.; Moreland, L.W.; Weaver, A.L.; et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N. Engl. J. Med.* **2000**, *343*, 1586–1593. [CrossRef] [PubMed]
- Catrina, A.I.; Trollmo, C.; af Klint, E.; Engstrom, M.; Lampa, J.; Hermansson, Y.; Klareskog, L.; Ulfgren, A.K. Evidence that anti-tumor necrosis factor therapy with both etanercept and infliximab induces apoptosis in macrophages, but not lymphocytes, in rheumatoid arthritis joints: Extended report. *Arthritis Rheum.* **2005**, *52*, 61–72. [CrossRef]
- Hodge, J.A.; Kawabata, T.T.; Krishnaswami, S.; Clark, J.D.; Telliez, J.-B.; Dowty, M.E.; Menon, S.; Lamba, M.; Zwillich, S. The mechanism of action of tofacitinib—An oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. *Clin. Exp. Rheumatol.* **2016**, *34*, 318–328.
- Chen, Y.-F.; Jobanputra, P.; Barton, P.; Jowett, S.; Bryan, S.; Clark, W.; Fry-Smith, A.; Burls, A. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. *Health Technol. Assess.* **2006**, *10*. [CrossRef]
- Aletaha, D.; Smolen, J. The definition and measurement of disease modification in inflammatory rheumatic diseases. *Rheum. Dis. Clin. N. Am.* **2006**, *32*, 9–44. [CrossRef]
- The DAS28 Score. Available online: <https://nras.org.uk/resource/the-das28-score/> (accessed on 15 January 2021).
- Aletaha, D.; Smolen, J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): A review of their usefulness and validity in rheumatoid arthritis. *Clin. Exp. Rheumatol.* **2005**, *23*, S100–S108.
- Linde, L.; Sorensen, J.; Ostergaard, M.; Horslev-Petersen, K.; Hetland, M. Does clinical remission lead to normalization of EQ-5D in patients with rheumatoid arthritis and is selection of remission criteria important? *J. Rheumatol.* **2010**, *37*, 285–290. [CrossRef]
- Provan, S.A.; Semb, A.G.; Hisdal, J.; Strandén, E.; Agewall, S.; Dagfinrud, H.; Angel, K.; Atar, D.; Kvien, T.K. Remission is the goal for cardiovascular risk management in patients with rheumatoid arthritis: A cross-sectional comparative study. *Ann. Rheum. Dis.* **2011**, *70*, 812–817. [CrossRef]
- Radner, H.; Amolen, J.; Aletaha, D. Remission in rheumatoid arthritis: Benefit over low disease activity in patient reported outcomes and costs. *Arthritis Res. Ther.* **2014**, *16*, R56. [CrossRef]

15. Romano, C.; Esposito, S.; Ferrara, R.; Cuomo, G. Tailoring biologic therapy for real-world rheumatoid arthritis patients. *Exp. Opin. Biol. Ther.* **2020**, *15*, 1–14. [[CrossRef](#)]
16. Li, N.; Betts, K.A.; Messali, A.J.; Skup, S.; Garg, V. Real-world Effectiveness of Biologic Disease-modifying Antirheumatic Drugs for the Treatment of Rheumatoid Arthritis After Etanercept Discontinuation in the United Kingdom, France, and Germany. *Clin. Ther.* **2017**, *39*, 1618–1627. [[CrossRef](#)] [[PubMed](#)]
17. Singh, S.; James, A.; Proudfoot, J.A.; Dulai, P.S.; Xu, R.; Feagan, B.G.; Sandborn, W.J.; Jairath, V. Comparative Efficacy and Speed of Onset of Action of Infliximab vs Golimumab in Ulcerative Colitis. *Clin. Gastroenterol. Hepatol.* **2019**, *18*, 424–431. [[CrossRef](#)] [[PubMed](#)]
18. Pelechas, E.; Voulgari, P.; Drosos, A. Golimumab for Rheumatoid Arthritis. *J. Clin. Med.* **2019**, *8*, 387. [[CrossRef](#)] [[PubMed](#)]
19. Kawalec, P.; Sladowska, K.; Malinowska, L.I.; Brzostek, T.; Kozka, M. European perspective on the management of rheumatoid arthritis: Clinical utility of tofacitinib. *Ther. Clin. Risk Manag.* **2017**, *14*, 15–29. [[CrossRef](#)]
20. Boyadzhieva, V.; Stoilov, N.; Ivanova, M.; Stoilov, R. Treatment of rheumatoid arthritis: csDMARDs versus bDMARDs. Prospective study to evaluate disease activity. *Revmatologiya* **2019**, *27*, 3–15. [[CrossRef](#)]
21. Boyadzhieva, V.V.; Stoilov, N.; Stoilov, R.M.; Tachkov, K.; Kamusheva, M.; Mitov, K.; Petrova, G.I. Quality of Life and Cost Study of Rheumatoid Arthritis Therapy with Biological Medicines. *Front. Pharmacol.* **2018**, *9*, 794. [[CrossRef](#)]
22. Boyadzhieva, V.; Stoilov, N.; Ivanova, M.; Petrova, G.; Stoilov, R. Real World Experience of Disease Activity in Patients with Rheumatoid Arthritis and Response to Treatment with Various Biologic DMARDs. *Front. Pharmacol.* **2018**, *9*, 1303. [[CrossRef](#)] [[PubMed](#)]
23. Tan, B.E.; Lim, A.L.; Kan, S.L.; Lim, C.H.; Tsang, E.E.L.; Chng, S.S.; Noor, N.M.; Jamid, N.M.; Teh, C.L.; Thundyil, R.J.; et al. Real-world clinical experience of biological disease modifying anti-rheumatic drugs in Malaysia rheumatoid arthritis patients. *Rheumatol Int.* **2017**, *37*, 1719–1725. [[CrossRef](#)] [[PubMed](#)]
24. Vieira, M.C.; Zwillich, S.; Jansen, J.P.; Smiechowski, B.; Spurden, D.; Wallenstein, G.V. Tofacitinib versus biologic treatments in patients with active rheumatoid arthritis who have had an inadequate response to tumor necrosis factor inhibitors: Results from a network meta-analysis. *Clin. Ther.* **2016**, *38*, 2628–2641. [[CrossRef](#)] [[PubMed](#)]
25. Wells, A.F.; Curtis, J.R.; Betts, K.A.; Douglas, K.; Du, E.X.; Ganguli, A. Systematic Literature Review and Meta-analysis of Tumor Necrosis Factor-Alpha Experienced Rheumatoid Arthritis. *Clin. Ther.* **2017**, *39*, 1680–1694.e2. [[CrossRef](#)]
26. Lee, Y.H.; Bae, S.C. Comparative efficacy and safety of tocilizumab, rituximab, abatacept and tofacitinib in patients with active rheumatoid arthritis that inadequately responds to tumor necrosis factor inhibitors: A Bayesian network meta-analysis of randomized controlled trials. *Int. J. Rheum. Dis.* **2016**, *19*, 1103–1111. [[CrossRef](#)]