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aProspective observational Cohort study to assess the impact of Biologics on health related quality of life in autoimmune diseases

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ABSTRACT

Objective : Objective: To assess and compare the impact of biologic agents used to treat rheumatoid arthritis (RA), inflammatory bowel diseases (IBD), and other autoimmune diseases on different domains of health-related quality of life—physical, psychological, mental, and social aspects of well-being that are influenced by disease.

Design : A prospective observational cohort study assessed the effect of biologic therapy on HRQOL for patients in Alexandria Main University Hospital, Alexandria, Egypt. It was conducted between December 2020 and August 2021. The drugs tested were Adalimumab-atto (Amjevita), a monoclonal anti-tumor necrosis factor alpha; Secukinumab (cosentyx), a monoclonal antibody to interleukin-17A; and Etanercept (Enbrel), a tumor necrosis factor (TNF) blocker. Adalimumab (humira) tumor necrosis factor (TNF) blockers, Infliximab (remicade) tumor necrosis factor (TNF)-alpha blockers, and Golimumab (simponi) tumor necrosis factor (TNF) inhibitors. Patient-reported outcomes on 70 participants were done using the validated Arabic version of the SF-36 questionnaire in the form of an oral interview to assess physical, social functioning, role limitations, emotional state, and general health.

Results: Patient outcomes for biologics on the 8 domains of the Short-Form questionnaire SF-36 are expressed by mean +/- SD; for physical functioning is 49.03+/-28.31 and median is 45, for role limitation due to physical health is 41.07 ± 39.02 and median is 25, for role limitation due to emotional problems is 51.43 ± 42.73 and median is 66.7, for energy/fatigue is 41.43 ± 16.94 and median is 45, for emotional wellbeing is 48.17 ± 18.20 and median is 52, for social functioning is 55.16 ± 24.86 and median is 62.5, for pain is 55.93 ± 21.56 and median is 55, for general health is 38.74 ± 13.64 and median is 40, for health change is 68.93 ± 25.34 and median is 75.

Conclusion: Infliximab showed significantly better results than Adalimumab and Etanercept regarding physical functioning. Infliximab also established a better outcome in role limitation due to physical health compared to Adalimumab-atto and Adalimumab. Also, Infliximab was significantly better than Adalimumab regarding energy and fatigue. Adalimumab-atto demonstrated a significantly better effect on energy and fatigue than its reference product, Adalimumab.

In rheumatoid arthritis cases, Adalimumab-atto had more favorable outcomes than its reference product, Adalimumab, in terms of energy, fatigue, and emotional well-being. While Etanercept demonstrated better pain management than Adalimumab..

Key word: biologics, autoimmune disease, health-related quality of life, SF36

Q 1: What is already known on this topic?

Biologics individually are known to be effective in improving HRQOL for patients with autoimmune disease.

Q2: What does this study add?

Our study demonstrates a comprehensive comparison between the drugs that help physicians make decisions about choosing between different biologics according to patients' tolerability, compliance, and satisfaction.

Q3: How might this study affect research practice or policy?

As our study compares different biologicals regarding health-related quality of life, we recommend HRQOL assessment be mandatory as routine flow-up work to individidlize patients' best therapy according to their needs and satisfaction; moreover, we need more frequent studies with a large sample size.

INTRODUCTION

Many chronic diseases have an impact on patients' quality of life. According to the CDC, HRQoL (health-related quality of life) is defined as "an individual's or a group's perceived physical and mental health over time" (1). Previously, most medical interventions and drug therapy were aimed at prolonging patients' lives. The modern approach also focuses on improving emotional and socioeconomic functioning. (1) Various diseases may not be fatal, but they consume a lot of health care resources and threaten the quality of life of the sufferers. (2)

The ways to assess HRQoL are scores and questionnaires; some are general and others are disease-specific, e.g. DAS-28(3), SF-36(4), and HAQ(5). A short-form questionnaire (SF-36) is an established tool to assess HRQoL in multiple disorders, such as ulcerative colitis. (6) Previously, many of the conventional treatments have failed to improve quality of life and relieve depression and anxiety associated with disease, despite being theoretically effective. The rise of biological therapies has made a huge leap forward in the disease prognosis and therapeutic options available. (7).

Because biologics work on only targeted steps in the inflammatory process instead of attacking the whole immune system, they often have fewer adverse effects than traditional therapies.(8) Biologics such as Adalimumab-atto (Adalimumab-atto), Infliximab (Infliximab), and others are widely used to treat different debilitating diseases such as Rheumatoid arthritis(9,10) , Psoriasis ((11), (12)), Crohn's disease ((13,14), Ulcerative colitis ((15,16), Ankylosing spondylitis, Behcet's disease, and different types of cancer.

MATERIALS AND METHODS

Patients:

This prospective observational cohort study assessed the effect of biologic therapy on HRQOL in patients from different departments in the Governmental Hospital, Alexandria, Egypt. It was conducted between December 2020 and August 2021.

The drugs tested were Adalimumab-atto (Adalimumab-atto), Secukinumab (Secukinumab), Etanercept (Etanercept), Adalimumab (Adalimumab), Infliximab (Infliximab), and Golimumab (Golimumab). Seventy patients were assessed, 54 females and 16 males with ages ranging from 24 to 75 years, using the validated Arabic version of the Short Form Health Survey SF-36 through oral interview to assess 36 items expressing physical and social functioning, role limitations, emotional state, and general health. Inclusion criteria:; exclusion criteria: Questionnaire. Statistical Analysis: Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp.) A descriptive analysis was conducted. Qualitative data were described using numbers and percents. The Kolmogorov-Smirnov test was used to verify the normality of the distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). The significance of the obtained results was judged at the 5% level. The used tests were the Kruskal-Wallis test for abnormally distributed quantitative variables to compare between more than two studied groups and the Post Hoc (Dunn's multiple comparisons test) for pairwise comparisons.

Inclusion criteria: patients on biologic treatment

Exclusion criteria: malignancy patients; pregnancy; ESRD; and end-stage liver disease..

Questionnaire:

The SF-36((17)) is a questionnaire that investigates eight health-related aspects: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. Scores resulting from each of the mentioned health-related aspects range from 0 to 100; the higher the score, the better the outcome

Statistical Analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp.) A descriptive analysis was conducted. Qualitative data were described using numbers and percents. The Kolmogorov-Smirnov test was used to verify the normality of the distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). The significance of the obtained results was judged at the 5% level.

The used tests were the Kruskal-Wallis test for abnormally distributed quantitative variables to compare between more than two studied groups and the Post Hoc (Dunn's multiple comparisons test) for pairwise comparisons.

RESULTS

Demographic characteristics of study data:

Seventy patients were interviewed; 77.1 percent were female and 22.9 percent were male. The mean age was 42.6 ± 12.8. Less than one-third suffered from co-morbidities requiring medication, such as hypertension, dyslipidemia, heart failure, and diabetes mellitus. All these conditions were controlled and didn't represent a potential confounding factor for the investigation.

Clinical characteristics of study data:

1- Distribution of the studied cases according to diagnosis in total cases (n = 70)

Rheumatoid arthritis represents 60% of the study population, 28.6% with Crohn's disease, 5.7% with ulcerative colitis, 4.3% with Behcet's, and 1.4% of the patients suffering from ankylosing spondylitis.

2- Distribution of the studied cases according to drug in total cases (n=70)

The drugs' contribution was 31.4% of the patients on Infliximab, 31.4% on Etanercept, 20% on Adalimumab-atto, 14.3% on Adalimumab, 1.4% on Secukinumab, and 1.4% on Golimumab.

3-Relation between drugs and diagnosis (n = 70)

Among 14 patients receiving Adalimumab-atto, 85.7% of them are suffering from rheumatoid arthritis, 7.1% with Behcet's, 7.1% with Crohn's, 22 patients on Etanercept were diagnosed with rheumatoid arthritis, 70% of Adalimumab cases were suffering from rheumatoid arthritis, 20% were Behcet's and 10% were Crohn's, 81.8% of the Infliximab cases were suffering from Crohn's and 18.2% from Ulcerative colitis.

Patient reported impact of biologics on SF-36 domains:

Table (1): Distribution of the studied cases (n = 70) according to different SF-36 domains

	Min. – Max.	**Median (IQR)**
Physical functioning	0.0 – 100.0	45.0 (30.0 – 75.0)
Role limitation due to physical health	0.0 – 100.0	25.0 (0.0 – 75.0)
Role limitation due to emotional problem	0.0 – 100.0	66.70 (0.0 – 100.0)
Energy/fatigue	10.0 – 80.0	45.0 (30.0 – 50.0)
Emotional well being	4.0 – 84.0	52.0 (32.0 – 64.0)
Social functioning	0.0 – 100.0	62.50(37.50 – 75.0)
Pain	10.0 – 100.0	55.0 (35.0 – 77.50)
General health	10.0 – 65.0	40.0 (30.0 – 50.0)
Health change	0.0 – 100.0	75.0 (50.0 – 75.0)

IQR: **Inter quartile range**   SD: **Standard deviation**

Drug-specific impacts on different parameters of HRQoL:

Table (2): Comparisons between drugs and SF36 domains in total cases (n = 70)

Percent of	Drugs						H	p
	Adalimumab-atto (n = 14)	Cosentyx (n = 1)	Etanercept (n = 22)	Adalimumab (n = 10)	Infliximab (n = 22)	Golimumab (n = 1)		
Physical functioning								
Min. – Max.	5.0 – 95.0		5.0 – 100.0	2.0 – 100.0	0.0 – 100.0		9.757[*]	0.021[*]
Median	37.50	55.0[#]	40.0	32.50	67.50	40.0[#]		
Sig. bet. Drugs	p_1=0.554,p_2=0.550,p_3=0.061,p_4=0.907,p_5=0.005[*],p_6=0.020[*]							
Role limitation due to physical health								
Min. – Max.	0.0 – 100.0		0.0 – 100.0	0.0 – 100.0	0.0 – 100.0		10.29[*]	0.016[*]
Median	0.0	50.0[#]	50.0	12.50	75.0	25.0[#]		
Sig. bet. Drugs	p_1=0.095,p_2=0.899,p_3=0.005[*],p_4=0.174,p_5=0.196,p_6=0.017[*]							
Role limitation due to emotional problem								
Min. – Max.	0.0 – 100.0		0.0 – 100.0	0.0 – 100.0	0.0 – 100.0		4.573	0.206
Median	66.70	100.0[#]	66.70	0.0	66.70	0.0[#]		
Energy/fatigue								
Min. – Max.	20.0 – 80.0		10.0 – 80.0	10.0 – 70.0	10.0 – 65.0		8.920[*]	0.030[*]
Median	45.0	65.0[#]	35.0	27.50	47.50	45.0[#]		
Sig. bet. Drugs	p_1=0.062,p_2=0.023[*],p_3=0.861,p_4=0.423,p_5=0.055,p_6=0.020[*]							
Emotional well being								
Min. – Max.	28.0 – 84.0		24.0 – 80.0	4.0 – 76.0	20.0 – 80.0		6.669	0.083
Median	58.0	56.0[#]	50.0	32.0	50.0	52.0[#]		

Percent of	Drugs						H	p
	Adalimumab-atto (n = 14)	Cosentyx (n = 1)	Etanercept (n = 22)	Adalimumab (n = 10)	Remicaide (n = 22)	Golimumab (n = 1)		
Social functioning								
Min. – Max.	25.0 – 100.0		12.50–100.0	0.0 – 87.50	12.50–100.0		4.222	0.238
Median	62.50	75.0#	62.25	37.50	62.50	37.50#		
Pain								
Min. – Max.	10.0 – 100.0		22.50 – 90.0	32.50 – 90.0	20.0 – 100.0		3.114	0.374
Median	55.0	67.5#	55.0	40.0	55.0	55.0#		
General health								
Min. – Max.	20.0 – 55.0		10.0 – 60.0	10.0 – 65.0	15.0 – 60.0		2.272	0.518
Median	45.0	45.0#	40.0	37.50	35.0	40.0#		
Health change								
Min. – Max.	25.0 – 100.0		25.0 – 100.0	50.0 – 100.0	0.0 – 100.0		0.428	0.934
Median	75.0	75.0#	75.0	75.0	75.0	50.0#		

H: H for **Kruskal Wallis test,** Pairwise comparison between each 2 groups was done using **Post Hoc Test (Dunn's for multiple comparisons test)**

P: p value for comparing between the studied drugs

p_1: p value for comparing between **Adalimumab-atto** and **Etanercept**

p_2: p value for comparing between **Adalimumab-atto** and **Adalimumab**

p_3: p value for comparing between **Adalimumab-atto** and **Infliximab**

p_4: p value for comparing between **Etanercept** and **Adalimumab**

p_5: p value for comparing between **Etanercept** and **Infliximab**

p_6: p value for comparing between **Adalimumab** and **Infliximab**

*: Statistically significant at $p \leq 0.05$

#: Excluded from the comparison due to small number of case (n = 1)

Physical functioning:

- There is statistically significant difference between Infliximab and Etanercept, favoring Infliximab and between Adalimumab and Infliximab, favoring Infliximab.

Role limitations due to physical functioning:

- There is statistically significant difference between Infliximab and Adalimumab-atto, favoring Infliximab and between Adalimumab and Infliximab, favoring Infliximab.

Energy/Fatigue:

- There is a statistically significant difference between Adalimumab-atto and Adalimumab, favoring Adalimumab-atto while comparison between Adalimumab and Infliximab, favoring Infliximab(P=0.02).

- In the remaining domains, no statistically significant differences were found.

Impact of drugs on disease specific parameters:

Rheumatoid Arthritis:

- Regarding rheumatoid cases (n=40) in table (3); there is a statistically significant difference between Adalimumab-atto and Adalimumab in energy/fatigue and in emotional well-being, favoring Adalimumab-atto.

- For pain management in table (3); the statistical significant difference between Etanercept and Adalimumab is favoring Etanercept.

- The remaining domains didn't show statistical significant difference among the tested drugs.

Crohn's disease:

Table (4) results are not reliable until availability and investigation of more cases.

Table (3): Comparison between drugs and SF36 domains in rheumatoid cases (n = 41)

Percent of	Drugs			H	p
	Adalimumab-atto (n = 12)	Etanercept (n = 22)	Adalimumab (n = 7)		
Physical functioning				4.565	0.102
Min. – Max.	5.0 – 85.0	5.0 – 100.0	2.0 – 35.0		
Median	35.0	40.0	15.0		
Role limitation due to physical health				5.352	0.069
Min. – Max.	0.0 – 75.0	0.0 – 100.0	0.0 – 50.0		
Median	0.0	50.0	25.0		
Role limitation due to emotional problem				3.225	0.199
Min. – Max.	0.0 – 100.0	0.0 – 100.0	0.0 – 100.0		
Median	50.0	66.70	0.0		
Energy/fatigue				8.847^*	0.012^*
Min. – Max.	20.0 – 65.0	10.0 – 80.0	10.0 – 45.0		
Median	45.0	35.0	25.0		
Sig. bet. Drugs	$p_1=0.105, p_2=0.003^*, p_3=0.056$				
Emotional well being				6.443^*	0.040^*
Min. – Max.	28.0 – 84.0	24.0 – 80.0	4.0 – 76.0		
Median	60.0	50.0	32.0		
Sig. bet. Drugs	$p_1=0.247, p_2=0.011^*, p_3=0.068$				

Percent of	Drugs			H	P
	Adalimumab-atto (n = 12)	Etanercept (n = 22)	Adalimumab (n = 7)		
Social functioning				4.912	0.086
Min. – Max.	25.0 – 75.0	12.50 – 100.0	0.0 – 75.0		
Median	62.50	62.25	25.0		
Pain				7.219*	0.027*
Min. – Max.	10.0 – 100.0	22.50 – 90.0	32.50 – 55.0		
Median	55.0	55.0	35.0		
Sig. bet. Drugs	p_1=0.272,p_2=0.109,p_3=0.008*				
General health				0.747	0.688
Min. – Max.	20.0 – 55.0	10.0 – 60.0	10.0 – 55.0		
Median	42.50	40.0	30.0		
Health change				0.028	0.986
Min. – Max.	25.0 – 100.0	25.0 – 100.0	50.0 – 100.0		
Median	75.0	75.0	75.0		

SD: **Standard deviation**

H: H for **Kruskal Wallis test,** Pairwise comparison between Each 2 groups was done using **Post Hoc Test (Dunn's for multiple comparisons test)**

p: p value for comparing between the studied drugs

p_1: p value for comparing between **Adalimumab-atto** and **Etanercept**

p_2: p value for comparing between **Adalimumab-atto** and **Adalimumab**

p_3: p value for comparing between **Etanercept** and **Adalimumab**

*: Statistically significant at p ≤ 0.05

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Table (4): Comparison between drugs and SF36 domains in Crohn's cases (n = 20)

Percent of	Drugs		
	Adalimumab-atto (n = 1)[#]	Adalimumab (n = 1)[#]	Infliximab (n = 18)
Physical functioning			
Min. – Max.	50.0[#]	100.0[#]	20.0 – 100.0
Median			62.50
Role limitation due to physical health			
Min. – Max.	0.0[#]	100.0[#]	0.0 – 100.0
Median			75.0
Role limitation due to emotional problem			
Min. – Max.	100.0[#]	100.0[#]	0.0 – 100.0
Median			66.70
Energy/fatigue			
Min. – Max.	50.0[#]	70.0[#]	10.0 – 65.0
Median			50.0
Emotional well being			
Min. – Max.	44.0[#]	64.0[#]	24.0 – 80.0
Median			54.0
Social functioning			
Min. – Max.	62.50[#]	87.50[#]	25.0 – 100.0
Median			75.0
Pain			
Min. – Max.	55.0[#]	90.0[#]	20.0 – 100.0
Median			55.0
General health			
Min. – Max.	55.0[#]	55.0[#]	15.0 – 60.0
Median			37.50
Health change			
Min. – Max.	75.0[#]	100.0[#]	0.0 – 100.0
Median			75.0

#: Excluded from the comparison due to small number of cases (n = 1)

DISCUSSION

The objective of the study was to provide clinical, functional information, and patient reported outcomes in reality settings among studied patients. A strength of our study is the simultaneous investigation of multiple drugs and multiple disorders, the relationships between them, and their impact on QoL. A short time and one study setting are considered study weaknesses. Through the study of 70 patients on biologics and their effect on HRQoL had been studied.

Infliximab proved significantly better results than Adalimumab and Etanercept regarding physical functioning. Infliximab established a better outcome in role limitation due to physical health compared to Adalimumab-atto and Adalimumab. Infliximab was significantly better than Adalimumab regarding energy and fatigue. This may be due to the fact that the majority of patients treated with Infliximab had Crohn's disease, which doesn't affect their physical functioning and health as much as in patients diagnosed with rheumatoid arthritis. So, the disease itself might be a factor. Results from other studies match our findings, as they find Infliximab improves most aspects of HRQoL within 8 weeks of therapy initiation up to 30 weeks of long-term maintenance therapy. ((6,18)) Another hypothesis may be due to the route of administration, as Infliximab was given in health care settings intravenously, which guarantees 100% drug bioavailability and an immediate distribution, while Adalimumab was administered subcutaneously at home which guarantees better compliance ((19))

The benefits of Adalimumab on HRQoL have been proven in multiple studies, as has its positive influence on work productivity. ((20), (21)). Interestingly, Adalimumab-atto demonstrated a significantly better effect on energy and fatigue than its reference product, Adalimumab. The reason for this unexpected result was not exactly known, but perhaps the patient's tolerability of the intrinsic nature of biologics. Biosimilars are products similar to the original drug in the active substance but not exactly the same because of differences in manufacturing details, including methods of purification. (22)

In rheumatoid arthritis cases, Adalimumab-atto had more favorable outcomes than its reference product, Adalimumab, in energy, fatigue, and emotional well-being((23,24).While Etanercept demonstrated better pain management than Adalimumab, this is unlike the results of an indirect comparison done between Etanercept and Adalimumab in the management of psoriasis, where adalimumab treatment for moderate to severe plaque psoriasis was associated with greater pain management, higher rates of resolution of skin signs and symptoms, and greater improvements in dermatological life quality. ((25)) In Crohn's cases, the results were unreliable. The superiority of one drug over another cannot be established until more patients are interviewed and more results are obtained.

Conclusion:

Infliximab showed better results than Adalimumab and Etanercept regarding physical functioning. Infliximab also established a better outcome in role limitation due to physical health compared to Adalimumab-atto and Adalimumab. Infliximab was significantly better than Adalimumab regarding energy and fatigue. Further research with a larger sample size will be needed to determine whether these results are disease-related or due to the drug itself. Adalimumab-atto demonstrated a significantly better effect on energy and fatigue than its reference product, Adalimumab, especially in rheumatoid arthritis cases, in addition to its effect on emotional well-being. Therefore, Adalimumab-atto may be better for depressed

patients. While Etanercept demonstrated better pain management than Adalimumab, suggesting it is a suitable option for patients with pain.

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