Are Biosimilars Equivalent To Originator Molecules In The Real-World? Assessments Of Efficacy, Toxicity, And Tolerability Of Infliximabs in Infliximab-Naïve Patients With Rheumatoid Arthritis.

Jasvinder A. Singh[1], Simon Helfgott[2], Kent Kwas Huston[3], Nehad Soloman[4], Andrew Frick[5], Scott Milligan[5], Colin Edgerton[6]

[1]University of Alabama at Birmingham, AL, USA, [2]Brigham and Women's Hospital, Harvard Medical School, MA, USA, [3]Kansas City Physician Partners, MO, USA, [4]Arizona Arthritis & Rheumatology Associates, P.C., AZ, USA, [5]Trio Health Analytics, CO, USA, [6]Articularis Healthcare, SC, USA

1. BACKGROUND

Biosimilar equivalence to originator molecules for efficacy, toxicity, and tolerability is a concern in real-world practice. Understanding the experience with existing biosimilars relative to originators is important as physicians and patients consider future treatment choices for optimal disease management.

2. METHODS

Data are specific to patients in care by the American Rheumatology Network, and reside in PIONEER Rheumatology, an enhanced database combining fielded EMR data with extracted information from open text (office visits, infusions logs, and provider-patient communications). Study population: Patients with rheumatoid arthritis with first infliximab exposure between Apr 2018 to Mar 2021 with >360 days history and >360 days follow up. Analyses: One-way ANOVA with post hoc Games-Howell (continuous), Pearson's chi-square with column proportions comparisons by z-test with Bonferroni correction (categorical), and time to event by Kaplan-Meier and log-rank test.

3. RESULTS

Of 569 study patients, 255 received INFLIXIMAB (IFX), 111 INFLIXIMAB-ABDA (ABDA), AND 203 INFLIXIMAB-DYYB (DYYB). Groups did not statistically differ by gender, baseline BMI, CDAI, DAS28, RAPID3, ALT, AST, and blood glucose, or concurrent use of csDMARD or corticosteroids, but did differ by race, age, payer coverage, baseline eGFR, and prior csDMARD treatment. [TABLE 1] With censor at 360 days, duration did not differ between groups with estimated mean (median) days to discontinuation equal to 258 (not reached) for IFX, 232 (259) for ABDA, and 236 (265) for DYYB (p=0.129). [FIGURE 1] For patients remaining on therapy for >180 days, disease assessments closest to 180 days but within +150 to +210 days while on therapy were available for 56% (93/166) IFX, 73% (41/56) ABDA, and 66% (78/118) DYYB. Significant differences in disease activity measures were not observed between treatment groups based on severity level distributions, mean scores, change in mean scores, or proportion of patients achieving reductions beyond the minimally important differences in scores. [TABLE 2] A second assessment for these patients examined the last observed disease assessments occurring >180 days but up to 360 days while on therapy. As with the assessments at 180 days, significant differences between treatment groups were not observed. [DATA NOT SHOWN] Discontinuation reasons extracted from visit notes were examined for the subset of patients who stopped treatment prior to 360 days from treatment start (n=277), and broadly classified into 3 groups: lack of efficacy, clinical conditions related or unrelated to treatment (adverse events, comorbidity development/worsening), and non-clinical reasons. Proportions of discontinuations by these classifications did not significantly differ between groups, nor did the choice of therapy following discontinuation significantly differ between groups. [TABLE 3]

4. CONCLUSION

In this study of infliximab-naïve patients, efficacy as recorded by disease assessments, toxicity as suggested by reasons for discontinuation, and tolerability as measured by persistency, did not statistically differ between biosimilars and the originator infliximab in community practice.

TABLE 1: Study population demographics at baseline (pre-index)

	(A) INFLIXIMAB n=255	(B) INFLIXIMAB-ABDA n=111	(C) INFLIXIMAB-DYYB n=203	TOTAL n=569	p
Female	203 (80%)	97 (87%)	165 (81%)	465 (82%)	0.204
Race					0.009
Black	11/208 (5%)	11/74 (15%)	21/144 (15%)	43/426 (10%)	A v. B,C
White	187/208 (90%)	63/74 (85%)	117/144 (81%)	3.67/426 (86%)	
Other	10/208 (5%)	0/74 (0%)	6/144 (4%)	16/426 (4%)	
Age, mean (SD)	57.9 (14.8)	58.7 (14.4)	61.4 (12.1)	59.3 (13.9)	0.022; A v. C
Age Groups					0.038
18-35	26 (10%)	10 (9%)	5 (2%)	41 (7%)	A,B v. C
36-49	41 (16%)	19 (17%)	27 (13%)	87 (15%)	
50-64	93 (36%)	32 (29%)	75 (37%)	200 (35%)	
65-74	61 (24%)	36 (32%)	66 (33%)	163 (29%)	
75+	34 (13%)	14 (13%)	30 (15%)	78 (14%)	
BMI, mean (SD)	31.3 (8.3) n=244	30.7 (8) n=110	31.4 (7.6) n=200	31.2 (8) n=554	0.752
BMI Group					0.463
<18.5	3/244 (1%)	1/110 (1%)	2/200 (1%)	6/554 (1%)	
18.5<25	46/244 (19%)	22/110 (20%)	44/200 (22%)	112/554 (20%)	
25<30	79/244 (32%)	33/110 (30%)	45/200 (23%)	157/554 (28%)	
30+	116/244 (48%)	54/110 (49%)	109/200 (55%)	279/554 (50%)	
Primary Payer Type					0.000
Commercial	154 (60%)	39 (35%)	84 (41%)	277 (49%)	A v. B,C
Medicaid	3 (1%)	26 (23%)	24 (12%)	53 (9%)	A v. B,C; B v. C
Medicare	94 (37%)	41 (37%)	86 (42%)	221 (39%)	
Tricare/VA	2 (1%)	2 (2%)	9 (4%)	13 (2%)	A v. C
Unknown	2 (1%)	3 (3%)	0 (0%)	5 (1%)	
Disease Assessments					
CDAI, mean (SD)	16.9 (12.4) n=119	18.9 (12.1) n=91	17.8 (13.1) n=138	17.7 (12.6) n=348	0.521
CDAI Groups					0.547
near remission (0-2.8)	11/119 (9%)	6/91 (7%)	10/138 (7%)	27/348 (8%)	
low (>2.8-10)	35/119 (29%)	17/91 (19%)	38/138 (28%)	90/348 (26%)	
moderate (>10-22)	40/119 (34%)	41/91 (45%)	52/138 (38%)	133/348 (38%)	
severe (>22-78)	33/119 (28%)	27/91 (30%)	38/138 (28%)	98/348 (28%)	
DAS28, mean (SD)	3.7 (1.4) n=147	4 (1.5) n=94	3.7 (1.4) n=159	3.8 (1.4) n=400	0.087
DAS28 Groups					0.102
near remission (0<2.6)	38/147 (26%)	15/94 (16%)	38/159 (24%)	91/400 (23%)	
low (2.6<3.2)	23/147 (16%)	18/94 (19%)	20/159 (13%)	61/400 (15%)	
moderate (3.2≤5.1)	62/147 (42%)	36/94 (38%)	77/159 (48%)	175/400 (44%)	
severe (>5.1-9.4)	24/147 (16%)	25/94 (27%)	24/159 (15%)	73/400 (18%)	
RAPID3, mean (SD)	3.9 (2.2) n=151	3.8 (2.5) n=61	3.6 (2.5) n=120	3.8 (2.3) n=332	0.680
RAPID3 Groups					0.178
near remission (0-1)	15/151 (10%)	12/61 (20%)	21/120 (18%)	48/332 (14%)	
low (>1-2)	23/151 (15%)	8/61 (13%)	18/120 (15%)	49/332 (15%)	
moderate (>2-4)	45/151 (30%)	10/61 (16%)	35/120 (29%)	90/332 (27%)	
severe (>4-10)	68/151 (45%)	31/61 (51%)	46/120 (38%)	145/332 (44%)	
Lab measures					
ALT U/L, mean (SD)	28.2 (19.6) n=214	23.1 (13.4) n=106	29.4 (31.7) n=194	27.6 (24.1) n=514	0.086
AST U/L, mean (SD)	23 (10) n=214	22.2 (13.6) n=106	23.3 (9.1) n=194	22.9 (10.5) n=514	0.706
eGFR mL/min, mean (SD)	84.8 (20) n=214	84.6 (19.9) n=106	78.3 (17.7) n=194	82.3 (19.3) n=514	0.001; A,B v. C
eGFR Groups					0.000
≥90	96/214 (45%)	38/106 (36%)	48/194 (25%)	182/514 (35%)	A v. C
≥60 and <90	91/214 (43%)	58/106 (55%)	119/194 (61%)	268/514 (52%)	A v. C
≥30 and <60	27/214 (13%)	9/106 (8%)	27/194 (14%)	63/514 (12%)	
≥15 and <30	0/214 (0%)	1/106 (1%)	0/194 (0%)	1/514 (0%)	
<15	0/214 (0%)	0/106 (0%)	0/194 (0%)	0/514 (0%)	
blood glc mg/dL, mean (SD)	109.3 (43.8) n=194	103.1 (31.6) n=103	104.9 (32.9) n=194	106.2 (37.4) n=491	0.315
Prior Treatments					
prior csDMARD	229 (90%)	107 (96%)	192 (95%)	528 (93%)	0.038; A v. B*
prior TNF	178 (70%)	75 (68%)	132 (65%)	385 (68%)	0.554
prior non-TNF bDMARD	69 (27%)	30 (27%)	40 (20%)	139 (24%)	0.148
prior tsDMARD	41 (16%)	14 (13%)	17 (8%)	72 (13%)	0.048; A v. C
Index Treatment					
+ csDMARD	190 (75%)	75 (68%)	152 (75%)	417 (73%)	0.315
+ corticosteroids	160 (63%)	60 (54%)	117 (58%)	337 (59%)	0.253

*Indicates that column proportions are significantly different by z-test only without Bonferroni correction.
DMARDs prefix abbreviations: cs (conventional synthetic), ts (targeted synthetic), b (biologic)

FIGURE 1: Patients remaining on therapy (Kaplan-Meier), censor at 360 days

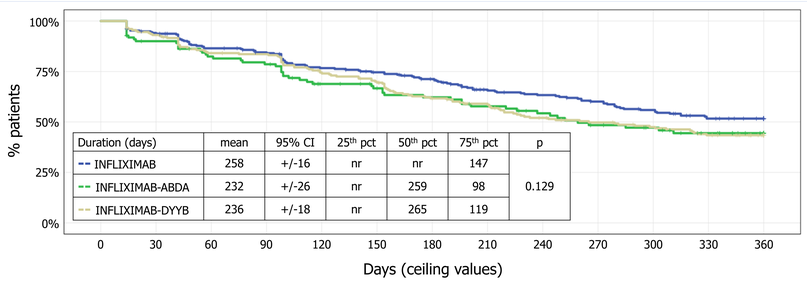

TABLE 2: During-therapy disease activity measures at 180 +/- 30 days

	(A) INFLIXIMAB	(B) INFLIXIMAB-ABDA	(C) INFLIXIMAB-DYYB	TOTAL	p
CDAI					0.159
near remission (0-2.8)	9/44 (20%)	1/28 (4%)	7/56 (13%)	17/128 (13%)	
low (>2.8-10)	13/44 (30%)	10/28 (36%)	25/56 (45%)	48/128 (38%)	
moderate (>10-22)	12/44 (27%)	7/28 (25%)	16/56 (29%)	35/128 (27%)	
severe (>22-78)	10/44 (23%)	10/28 (36%)	8/56 (14%)	28/128 (22%)	
CDAI, mean (SD)	13.3 (11.7)	16.5 (10.3)	11.3 (8.6)	13.1 (10.3)	0.087
CDAI, mean (SD) difference from pre-index	-4.7 (11.5) n=37	0.1 (14.6) n=26	-6 (10.1) n=47	-4.2 (11.9) n=110	0.103
CDAI, % with MID* from pre-index	17/37 (46%)	7/26 (27%)	22/47 (47%)	46/110 (42%)	0.211
DAS28					0.326
near remission (0<2.6)	27/73 (37%)	6/38 (16%)	21/73 (29%)	54/184 (29%)	
low (2.6<3.2)	12/73 (16%)	7/38 (18%)	17/73 (23%)	36/184 (20%)	
moderate (3.2≤5.1)	26/73 (36%)	20/38 (53%)	28/73 (38%)	74/184 (40%)	
severe (>5.1-9.4)	8/73 (11%)	5/38 (13%)	7/73 (10%)	20/184 (11%)	
DAS28, mean (SD)	3.2 (1.3)	3.7 (1.2)	3.3 (1.3)	3.3 (1.3)	0.147
DAS28, mean (SD) difference from pre-index	-0.5 (1.5) n=63	-0.4 (1.4) n=37	-0.4 (1.2) n=69	-0.4 (1.3) n=169	0.957
DAS28, % with MID* from pre-index	16/63 (25%)	10/37 (27%)	17/69 (25%)	43/169 (25%)	0.964
RAPID3 Groups					0.152
near remission (0-1)	7/37 (19%)	4/17 (24%)	8/30 (27%)	19/84 (23%)	
low (>1-2)	1/37 (3%)	4/17 (24%)	5/30 (17%)	10/84 (12%)	
moderate (>2-4)	14/37 (38%)	3/17 (18%)	11/30 (37%)	28/84 (33%)	
severe (>4-10)	15/37 (41%)	6/17 (35%)	6/30 (20%)	27/84 (32%)	
RAPID3, mean (SD)	3.6 (2.2)	2.7 (2.1)	2.7 (2.1)	3.1 (2.2)	0.194
RAPID3, mean (SD) difference from pre-index	-0.2 (2.2) n=33	-0.6 (1.4) n=10	-0.7 (2.3) n=26	-0.5 (2.1) n=69	0.666
RAPID3, % with MID* from pre-index	9/33 (27%)	2/10 (20%)	6/26 (23%)	17/69 (25%)	0.872

*MID or minimally important difference defined as: CDAI >12 when starting CDAI >22, >6 when starting CDAI 10–22, and >1 when starting CDAI <10; DAS28 >1.2; RAPID3 >1.27 on 10-point scale.

Table 3: Discontinuation Reasons and Next Drug

	INFLIXIMAB	INFLIXIMAB-ABDA	INFLIXIMAB-DYYB	Grand Total	p
Discontinuation Reason Groups*					
Lack of Efficacy	47/114 (41%)	20/54 (37%)	35/109 (32%)	102/277 (37%)	0.369
Clinical Condition†	71/114 (62%)	30/54 (56%)	64/109 (59%)	165/277 (60%)	0.690
Non-clinical Reason	30/114 (26%)	21/54 (39%)	28/109 (26%)	79/277 (29%)	0.170
Unspecified	8/114 (7%)	3/54 (6%)	12/109 (11%)	23/277 (8%)	0.400
Next Drug#					0.269
Different infliximab	30/114 (26%)	16/54 (30%)	21/109 (19%)	67/277 (24%)	
Non-infliximab TNF	11/114 (10%)	9/54 (17%)	19/109 (17%)	39/277 (14%)	
Non-TNF bDMARD	16/114 (14%)	8/54 (15%)	25/109 (23%)	49/277 (18%)	
tsDMARD	14/114 (12%)	5/54 (9%)	7/109 (6%)	26/277 (9%)	
csDMARD	24/114 (21%)	10/54 (19%)	16/109 (15%)	50/277 (18%)	
None (not initiated in window)	19/114 (17%)	6/54 (11%)	21/109 (19%)	46/277 (17%)	

*Multiple reasons may be indicated for each discontinuation and as such, these are overlapping categories. #Next Drug distributions are of mutually exclusive groups. csDMARD indicated only if present and other drug classes absent. †Clinical condition defined as adverse events, worsening of existing comorbidities, and/or development of comorbidities, but separate from condition stemming from uncontrolled RA (i.e., lack or loss of efficacy).

One or more authors provided services to and/or received compensation from Abbvie, Adaptimmune Therapeutics, Adept Field Solutions, Amarin, American College of Rheumatology, Amgen, AstraZeneca, Atyu Biopharma, Boehringer-Ingelheim, BMS, Clearview Healthcare, Clinical Care Options, Crealta/Horizon Enzolytics Inc., FDA Arthritis Advisory Committee, Focus Forward, GeoVax Labs, Gilead, GSK, Intuitive Surgical Inc./Philips Electronics North America, Janssen, Jupiter Life Science, Lilly, MedIQ, Medisys, Medscape, Moderna Pharmaceuticals, National Institutes of Health, Navigant, Novartis, Outcomes Measures in Rheumatology (OMERACT), Pfizer, Pieris Pharmaceuticals, PK Med, Practice Point Communications, Putnam Associates, Sandoz, Schipher, Seres Therapeutics, Simply Speaking, Spherix, Tonix Pharmaceuticals Holding Corp, TPT Global Tech, Trio Health, Two Labs Inc., UBM LLC, UCB, Vaxart Pharmaceuticals, Veterans Affairs Rheumatology Field Advisory Board (FAB), Viking Therapeutics, WebMD, and Zimmer Biomet Holdings.