

SUPPLEMENTARY INFORMATION

Table S1. Results of randomized controlled trials (RCTs) of biologicals and small molecule JAK inhibitors compared to placebo in methotrexate inadequate responders

Intervention	MOA	Follow-up (weeks)	ACR 50 (%)	Trial
Adalimumab	anti-TNF	24	55%	Weinblatt, ARMADA [61]
Adalimumab	anti-TNF	52	42%	Keystone [62]
Certolizumab	anti-TNF	52	37%	Keystone, RAPID 1 [63]
Certolizumab	anti-TNF	24	33%	Smolen, RAPID 2 [64]
Etanercept	anti-TNF	24	40%	Moreland [65]
Golimumab	anti-TNF	16	37%	Kay [66]
Golimumab	anti-TNF	14	35%	Keystone, GO FORWARD [67]
Infliximab	anti-TNF	30	27%	Maini, ATTRACT [68]
Infliximab	anti-TNF	14	31%	Abe [69]
Abatacept	IL-6	52	40%	Kremer, AIM [70]
Abatacept	IL-6	52	42%	Kremer [71]
Rituximab	B-Cell	12	43%	Edwards [72]
Rituximab	B-Cell	24	34%	Emery, DANCER [73]
Tocilizumab	IL-6	24	44%	Smolen, OPTION [74]
Tocilizumab	IL-6	16	53%	Maini, CHARISMA [75]
Tofacitinib	JAKi	24	32%	van der Heijde, ORAL SCAN [76]
Baricitinib	JAKi	12	35%	Keystone [77]
Average First line all MOA		27	39%	
Average First line no anti-TNF		27	40%	

Table S2. Results of randomized controlled trials of biologics and small molecule JAK inhibitors compared to placebo in TNF inadequate responders

Intervention	MOA	Follow-up (weeks)	ACR 50 (%)	Trial
Golimumab	anti-TNF	24	16%	Smolen, GO AFTER [78]
Abatacept	IL-6	24	20%	Genovese, ATTAIN [79]
Rituximab	B-Cell	24	26%	Emery, SERENE [80]
Tocilizumab	IL-6	24	29%	Emery, RADIATE [81]
Tofacitinib	JAK	12	27%	Burmester, ORAL Step [82]
Average Second line all MOA		22	24%	
Average Second line no anti-TNF		22	26%	

Table S3. Response rates for second line anti-TNF therapy cycling and other MOAs

Intervention	ACR50 (%)	Usage
anti-TNF	16%	60%
Other MOA (average)	26%	40%
Weighted average	20%	

Table S4. Biologic drug pharmacy cost from the payer perspective. Total biologic costs include the total biologic drug and associated administration costs, based on the actual drug utilization and drug administrations.

Biologic	MOA	Drug Cost	Usage
Abatacept	T cell	\$ 42,306	38%
Rituximab	B cell	\$ 30,746	54%
Tocilizumab	IL-6	\$ 27,627	8%
MOA Weighted Average		\$ 34,906.98	12 months
		\$ 17,453.49	6 months
etanercept	Anti-TNF	\$ 40,422	50%
adalimumab	Anti-TNF	\$ 40,415	32%
infliximab	Anti-TNF	\$ 28,906	11%
Golimumab	Anti-TNF	\$ 34,863	4%
Certolizumab	Anti-TNF	\$ 34,775	3%
anti-TNF Weighted Average		\$ 38,728.32	12 months
		\$ 19,364.16	6 months
Second Line			
anti-TNF		\$ 38,728	60%
MOA		\$ 34,907	40%
Weighted Average with TNF Cycling		\$ 37,199.78	12 months
		\$ 18,599.89	6 months

Table S5. Total Medical and Pharmacy Costs. Total medical cost include inpatient hospitalizations, joint replacement surgeries, infections, CV events, ED encounters, outpatient visits, physician office visits, rheumatologist office visits, physical/occupational therapy, durable medical equipment, and imaging such as radiographs, magnetic resonance imaging and other types of imaging. Non-biologic pharmacy costs include all-cause pharmacy costs include all costs related to outpatient pharmacy fills, with the exception of fills for biologic drugs.

Costs	12 months	6 months
Responders		
Medical Costs	\$ 7,581	\$ 3,791
Pharmacy excluding biologic	\$ 1,698	\$ 849
Inadequate responders		
Medical Costs	\$ 13,318	\$ 6,659
Pharmacy excluding biologic	\$ 2,052	\$ 1,026

Table S6. Definition of PrismRA result

PrismRA result	Likelihood of inadequate response to anti-TNF therapy	Inadequate response signal detection
≥16.6	≥95%	Very high
≥11.5	≥90%	High
≥9.4	≥85%	Moderate
<9.4	N/A	Not detected

Table S7. Assessment of disease measures stratified by PrismRA signal of inadequate response to anti-TNF therapies

Metric	Timepoint	PrismRA likelihood of non-response	N	Mean	Standard deviation
DAS28-CRP	Baseline	Very High	47	5.17	0.83
		High	26	4.87	0.92
		Moderate	9	5.18	0.88
		Low	93	4.91	1.04
	6 months	Very High	46	3.95	1.24
		High	22	3.48	1.40
		Moderate	8	2.96	1.26
		Low	88	3.05	1.31
Tender joint count	Baseline	Very High	47	13.32	7.16
		High	26	12.40	7.6
		Moderate	9	10.82	7.18
		Low	93	11.40	7.28
	6 months	Very High	47	8.09	7.16
		High	26	5.87	7.22

		Moderate	9	2.59	2.87
		Low	93	5.01	6.80
Swollen joint count	Baseline	Very High	47	8.19	5.57
		High	26	7.11	5.37
		Moderate	9	10.43	5.10
		Low	93	8.18	5.64
	6 months	Very High	47	4.72	5.24
		High	26	3.53	4.30
		Moderate	9	1.69	2.10
		Low	93	2.57	3.52
CDAI	Baseline	Very High	47	33.68	13.10
		High	26	30.51	12.11
		Moderate	9	32.88	11.11
		Low	93	29.65	12.61
	6 months	Very High	47	20.64	12.81
		High	26	16.67	13.35
		Moderate	9	9.33	7.13
		Low	92	12.83	11.75

Table S8. Number of patients reaching endpoints stratified by PrismRA signal of inadequate response to anti-TNF therapies

		Other	LDA	Remission
DAS28-CRP	Very High	35	5	6
	high	16	0	6
	Moderate	4	1	3
	Low	48	5	35

		Other	EULAR good response
EULAR good	Very High	38	9
	high	20	6
	Moderate	6	3
	Low	56	37

Table S9. Odds of inadequate response to anti-TNF therapies

Clinical metric	OR (95% CI)
PrismRA	6.58 (2.75, 15.6)
Female sex	2.42 (1.20, 4.88)
BMI ≥ 30 kg/m ² (obese)	2.01 (1.00, 4.04)
Number of swollen joints	1.92 (0.98, 3.71)
CDAI	1.45 (0.70, 3.01)
Any tobacco smoke (current or previous)	1.13 (0.59, 2.18)
Age > 50 years	0.84 (0.43, 1.68)
Number of tender joints	0.75 (0.39, 1.45)
Clinical metrics algorithm	1.34 (0.67, 2.34)