

Biologic Drugs for Rheumatoid Arthritis in the Medicare Program: A Cost Effectiveness Analysis: *Arthritis and Rheumatism*: In press.

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Appendix

Description of statistical models

Appendix Table 1 shows the coefficients and standard deviations for the following statistical models.

Statistical Model 1a: Log probability of achieving ACR20/50 response - methotrexate

Statistical Model 1b: Log odds model of achieving ACR20/50 response – biologic plus methotrexate

In order to estimate the probability of ACR20/50 response for a patient on a single biologic in conjunction with methotrexate:

$$p_i = p_{mtx} \times OR_i / (1 - p_{mtx} \times (1 - OR_i))$$

where p = probability, OR = odds ratio, i = anakinra, etanercept, infliximab, adalimumab, mtx = methotrexate

Statistical model 2: Multivariate regression model to predict HAQ-DI 6 months after starting biologic treatment

To predict HAQ-DI at six months (h_6) from baseline (h_0) using logit transformations to map the real line to 0:3 range

$$h_6 = l^{-1}(\alpha + \beta l(h_0) + \gamma^T x)$$

where h_6 is HAQ-DI at 6 months post biologic treatment, l is the logit function, α is the constant, β is the intercept for baseline HAQ-DI (h_0), and γ are the coefficients on covariates x_1 to x_n .

Statistical model 3: Multivariate regression model to predict HAQ-DI post 6 months after starting biologic treatment

To predict HAQ-DI at 6, 12, ...etc. months ($h(t)$) after 6 month HAQ-DI (h_a) using logit transformations to constrain to 0:3 range

$$l(h(t)) = l(h_a) + t(\delta + \gamma^T x)$$

Where l = logit function, h_a is six month HAQ-DI, t = time in months between h_a and current HAQ-DI observation and γ are the coefficients on covariates x_1 to x_n

Statistical model 4: Multivariate Weibull survival analysis to predict time on 1st biologic treatment

The baseline hazard function is

$$h_0(t) = \frac{\alpha}{\beta^\alpha} t^{\alpha-1}$$

Where α is the shape, β the scale parameter and t is the time in months. A proportional hazards model is fitted, adjusting the survival for covariates.

$$h(t) = h_0(t) \exp(\gamma^T x)$$

Where γ are the coefficients for covariates x_1 to x_{12}

The survival curve is

$$s(t) = \exp\left(-\int_0^t h(u)du\right)$$

$$= \exp\left(-\exp(\gamma^T x)\left(\frac{t}{\beta}\right)^\alpha\right)$$

Statistical model 5: Multivariate regression model to predict HAQ-DI after withdrawal from biologic therapy

To predict HAQ-DI at 6, 12,...etc. months ($h(t)$) after HAQ-DI at withdrawal (h_b) using logit transformations to constrain to 0:3 range

$$l(h(t)) = l(h_b) + t(\delta + \gamma^T x)$$

Where l = logit function, h_b is six month HAQ-DI, t = time in months between h_b and current HAQ-DI observation and γ are the coefficients on covariates x_1 to x_n

Statistical model 6: Multivariate regression model to estimate EQ5D utility.

And in sensitivity analysis,

Statistical model 9: Multivariate regression model to estimate SF6D utility.

To estimate utility using the EQ5D (SF6D) tariff the following regression was estimated using logit transformations to constrain to -0.6: 1 utility range for EQ5D and 0.29: 1 utility range for SF6D:

$$l(u(h)) = \alpha + \gamma^T x + \varepsilon$$

Statistical model 7: Generalized Linear Model (GLM) of Medicare resource use by HAQ-DI

To estimate resource use (r) per 6 month period in 2005 US dollars a generalised linear models (GLMs) with gamma transformation is used to transform the expected skewed cost distribution

FOR SENSITIVITY ANALYSIS

Statistical model 8: Proportional odds cumulative logit model for predicting 6 month HAQ-DI response

Let π_1 π_2 and π_3 be the probability of a HAQ response 0 (less than 20%), 1 (between 20 and 50%) or 2 (greater than 50%)

$$L_1 = \log\left(\frac{\pi_1}{1-\pi_1}\right)$$

$$L_2 = \log\left(\frac{\pi_1 + \pi_2}{1-(\pi_1 + \pi_2)}\right)$$

We fit the model

$$L_j = \alpha_j - \gamma^T x$$

To predict the probability of a HAQ response we use the equations

$$P(\text{HAQ}=1) = 1 - \frac{1}{1 + e(\gamma^T x - \alpha_1)}$$

$$P(\text{HAQ}=2) = 1 - \frac{1}{1 + e(\gamma^T x - \alpha_2)}$$

where γ are the coefficients for the covariates and α_1, α_2 are the cut points. The probability of a HAQ1 response is the probability of achieving at least a HAQ20% improvement i.e. this includes those that achieve a 50% or better response.

Appendix Table 1: Statistical Models

Statistical model 1a: Logit model to predict probability of ACR20/ACR50 response at 6 months on methotrexate		sd	
ACR20			
	Methotrexate	-0.525	0.225
	Disease duration - mean disease duration observed in studies	-0.164	0.048
	Baseline HAQ-DI - mean baseline HAQ-DI observed in studies	2.708	1.644
ACR50			
	Methotrexate	-1.737	0.224
	Disease duration - mean disease duration observed in studies	-0.203	0.046
	Baseline HAQ-DI - mean baseline HAQ-DI observed in studies	3.082	1.566
Statistical model 1b: Log odds model to predict ACR20/50 response on biologic			
ACR20			
	Anakinra	0.581	0.190
	Etanercept	1.259	0.198
	Infliximab	1.239	0.202
	Adalimumab	1.121	0.150
	Disease duration - mean disease duration in studies	0.111	0.022
	Baseline HAQ-DI - mean baseline HAQ-DI in studies	-0.965	0.640
ACR50			
	Anakinra	0.802	0.253
	Etanercept	1.468	0.238
	Infliximab	1.397	0.232
	Adalimumab	1.385	0.173
	Disease duration - mean disease duration in studies	0.115	0.026
	Baseline HAQ-DI - mean baseline HAQ-DI in studies	-1.671	0.781
Statistical model 2: Multivariate regression model to predict HAQ-DI 6 months after starting biologic treatment			
x_1	age	0.001	0.004
x_2	Disease duration (yrs)	-0.002	0.003
x_3	Index of co-morbidities	0.002	0.015
x_4	HAQ-DI at baseline	0.821	0.029
x_5	Male	-0.119	0.071
x_6	On DMARD as well as biologic	-0.025	0.074
x_7	Number of previous DMARDs	-0.009	0.016
x_9	Not on Medicare	Reference	
x_9	Medicare 1(over 65)	-0.039	0.116
x_9	Medicare 2 (disability)	-0.010	0.089
x_{10}	Total income	0.000	0.000
x_{11}	Years of education	0.014	0.013
x_{12}	Ethnicity - white	-0.035	0.104
x_{13}	Not ACR20 responder	Reference	
x_{13}	ACR20 responder	-0.860	0.071
x_{13}	ACR50 responder	-2.463	0.096
α	Constant	0.069	0.287
Statistical model 3: Multivariate regression model to predict HAQ-DI post 6 months after starting biologic treatment			
t	time	-0.013	0.012
tx_1	age	0.000	0.000
tx_2	Disease duration (yrs)	0.000	0.000

tx_3	Index of co-morbidities	0.001	0.001
tx_4	HAQ-DI at baseline	-0.003	0.001
tx_5	Male	0.001	0.003
tx_6	On DMARD as well as biologic	0.002	0.002
tx_7	Number of previous DMARDs	0.001	0.001
tx_9	Not on Medicare	Reference	
tx_9	Medicare 1(over 65)	0.001	0.002
tx_9	Medicare 2 (disability)	-0.002	0.004
tx_{10}	Total income	0.000	0.000
tx_{11}	Years of education	0.001	0.000
tx_{12}	Ethnicity - white	-0.003	0.004

Statistical model 4: Multivariate Weibull survival analysis to predict time on 1st biologic treatment

x_1	age	0.009	0.004
x_2	Disease duration (yrs)	0.007	0.003
x_3	Index of co-morbidities	0.098	0.016
x_4	HAQ-DI at baseline	0.000	0.048
x_5	Male	-0.086	0.078
x_6	On DMARD as well as biologic	-0.006	0.082
x_7	Number of previous DMARDs	0.006	0.018
x_8	Etanercept	Reference	
x_8	Infliximab	0.080	0.064
x_8	Anakinra	1.212	0.148
x_8	Adalimumab	0.016	0.190
x_9	Not on Medicare	Reference	
x_9	Medicare 1(over 65)	0.130	0.125
x_9	Medicare 2 (disability)	-0.077	0.101
x_{10}	Total income	0.000	0.000
x_{11}	Years of education	-0.001	0.013
x_{12}	Ethnicity - white	-0.238	0.106
$Ln \alpha$	Constant	-4.517	0.323
$Ln p$	Log shape	-0.055	0.024

Statistical model 5: Multivariate regression model to predict HAQ-DI after withdrawal from biologic therapy

t	time	-0.043	0.019
tx_1	age	0.000	0.000
tx_2	Disease duration (yrs)	0.000	0.000
tx_3	Index of co-morbidities	0.001	0.001
tx_4	HAQ-DI at baseline	-0.002	0.001
tx_5	Male	0.001	0.006
tx_6	On DMARD as well as biologic	0.007	0.003
tx_7	Number of previous DMARDs	0.001	0.001
tx_9	Not on Medicare	Reference	
tx_9	Medicare 1(over 65)	-0.003	0.004
tx_9	Medicare 2 (disability)	-0.006	0.006
tx_{10}	Total income	0.000	0.000
tx_{11}	Years of education	0.000	0.001
tx_{12}	Ethnicity - white	-0.003	0.005

Statistical model 6: Multivariate regression model to estimate EQ5D utility.

x_1	age	0.006	0.000
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x_2	Disease duration (yrs)	0.002	0.000
x_4	HAQ-DI at baseline	-0.200	0.010
x_5	Male	-0.291	0.012
x_7	Number of previous DMARDs	0.025	0.003
x_{13}	Current HAQ-DI	-0.865	0.010
K	Constant	2.073	0.026

Statistical model 7: Generalized Linear Model (GLM) of Medicare resource use by HAQ-DI

x_1	Age	-2.120	4.700
x_2	Disease duration (yrs)	1.400	2.200
x_3	Index of co-morbidities	207.4	17.50
x_4	HAQ-DI at baseline	-204.7	58.00
x_{13}	Current HAQ-DI	759.5	52.70
x_5	Male	230.6	65.50
x_6	On DMARD as well as biologic	-169.3	70.60
x_7	Number of previous DMARDs	122.8	20.50
x_8	Not on biologic	Reference	
x_8	Etanercept	-78.84	139.9
x_8	Infliximab	49.98	119.7
x_8	Anakinra	-1252	215.6
x_8	Adalimumab	-500.5	234.1
x_9	Not on Medicare	Reference	
x_9	Medicare 1(over 65)	63.18	144.7
x_9	Medicare 2 (disability)	55.37	94.20
x_{10}	Total income	0.000	0.000
x_{11}	Years of education	9.320	11.80
x_{12}	Ethnicity – white	-56.82	120.0
K	Constant	588.1	351.1

Statistical model 8: Proportional odds cumulative Logit model for predicting type of 6 month HAQ-DI response

x_1	age	-0.011	0.016
x_2	Disease duration (yrs)	-0.018	0.013
x_3	Index of co-morbidities	-0.184	0.078
x_4	HAQ-DI at baseline	-0.430	0.230
x_5	Male	0.225	0.328
x_6	On DMARD as well as biologic	0.224	0.375
x_7	Number of previous DMARDs	-0.047	0.078
x_8	Etanercept	Reference	
x_8	Infliximab	-0.331	0.275
x_8	Anakinra	-0.313	0.698
x_8	Adalimumab	-0.025	0.633
x_9	Not on Medicare	Reference	
x_9	Medicare 1(over 65)	0.177	0.619
x_9	Medicare 2 (disability)	0.322	0.425
x_{10}	Total income	0.000	0.000
x_{11}	Years of education	-0.054	0.061
x_{12}	Ethnicity - white	-0.889	0.450
α_1	<HAQ20% 20-50% or >50% intercept	-1.823	1.353
α_2	<HAQ20% or 20-50% >50% intercept	-0.451	1.349

Statistical model 9: Multivariate regression model to estimate SF6D utility.

x_1	age	0.004	0.001
x_2	Disease duration (yrs)	0.003	0.001
x_4	HAQ-DI at baseline	-0.202	0.010
x_5	Male	-0.025	0.018
x_7	Number of previous DMARDs	0.007	0.004
x_{13}	Current HAQ-DI	-0.552	0.011
K	Constant	0.509	0.037
