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COMPARED EFFICACY OF RITUXIMAB, ABATACEPT, AND TOCILIZUMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS REFRACTORY TO METHOTREXATE OR ANTI-TNF AGENTS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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BACKGROUND

Disease-modifying antirheumatic drugs (DMARDs), especially methotrexate (MTX) and the biological (bDMARDs) class of tumor necrosis-factor inhibitors have improved the treatment of rheumatoid arthritis (RA), but 1/3 of individuals do not respond to this treatment. Rituximab, abatacept, and tocilizumab are bDMARD options available, but it is unclear whether any of these is superior to the others. The objective of this work was to compare the efficacy of rituximab, tocilizumab, and abatacept in individuals with RA refractory to MTX or anti-TNF.

METHODS

It is a phase 2-4 randomized controlled trials (RCTs) evaluating patients with RA refractory to MTX or anti-TNF treated with rituximab, abatacept, and tocilizumab compared to controls. Study characteristics, quality, and data were independently assessed by two investigators, in PubMed, Cochrane Library, Embase, Web of Science, Scopus, and LILACS until July 18, 2020. The primary outcome was achieving ACR70 response.

RESULTS

The meta-analysis included 19 RCTs, with 7,835 patients randomized to the intervention versus control and a mean study duration of 1.2 year. The mean age was 52.3 years, 77.2% were women, and the mean disease duration was 8.7 years. The hazard ratios (HRs) for achieving an ACR70 response at 6 months were not different among the bDMARDs when compared to placebo (Table 1); however, there was a high heterogeneity. Three factors showing a critical imbalance among the bDMARD classes: baseline HAQ score, study duration, and frequency of anti-TNF treatment in the control arm. To understand the heterogeneity among RCTs, multivariate meta-regression adjusted to these three factors were conducted for the relative risk (RR) for achieving an ACR70 during the study follow-up. Thus, heterogeneity was attenuated ($I2 = 24\%$, p for heterogeneity = 0.27) and the explanatory power of the model increased ($R2 = 85\%$). In this model, rituximab did not modify the chance of achieving an ACR70 compared to abatacept (RR = 1.773, 95% CI = 0.113–10.21, p = 0.765). In contrast, abatacept was associated with a RR = 2.217 (95% CI = 1.554–3.161, $p < 0.001$) for ACR70 compared to tocilizumab (Table 2).

Table 1. Indirect comparisons among bDMARDs.

	ACR70 response rate, HR (95% CI), p value	
	All trials	Excluding one trial from each class*
Abatacept vs. rituximab	1.017 (0.373, 2.845). p = 0.84	1.029 (0.324, 2.959), p = 0.88
Tocilizumab vs. rituximab	0.791 (0.254, 2.461), p = 0.32	0.811 (0.224, 2.618), p = 0.40
Tocilizumab vs. abatacept	0.806 (0.263, 2.505), p = 0.37	0.814 (0.237, 2.614), p = 0.43
Abatacept vs. anti-TNF	1.043 (0.422, 2.242), p = 0 59	1.063 (0.402, 2.492), p = 0.56
Tocilizumab vs. anti-TNF	0.839 (0.373, 3.804), p = 0 45	0.814 (0.331, 4.007), p = 0.41
Rituximab vs. anti-TNF	1.059 (0339, 2.581), p = 0.51	1.042 (0.305, 2.886), p = 0.67
Abatacept vs. placebo	3.423 (1.422, 8.709), p < 0 001	3.438 (1.413, 8.762), p < 0.001
Tocilizumab vs. placebo	2.765 (1.240, 6.692), p = 0.009	2.525 (1.096, 6.921). p = 0.015
Rituximab vs. placebo	3.494 (1.530, 8.658), p < 0.001	3.509 (1.522, 8.676), p < 0.001

Table 2. Meta-regression models for achieving ACR70.

	RR	95% CI		p
		Lower bound	Upper bound	
Model 1				
Mean baseline HAQ (each additional 0.1 pd)	2.0433	1.0328	14.4460	0.028
Model 2				
Background anti-TNF in control arm (yes vs no)	0.3166	0.1345	0.7460	0.009
Model 3				
Follow-up time (each additional 1 month)	0.9714	0.9522	0.9920	0.007
Model 4				
Mean baseline HAQ (each additional 0.1 point)	2.0332	1.0141	14.6164	0.045
Background anti-TNF in control arm (yes vs. no)	0.2187	0.1341	0.3567	< 0.001
Follow-up time (each additional 1 month)	0.9763	0.9504	9899	0.016
ABA vs RTX	1.7736	0.1134	102.165	0.625
ABA vs TCZ	2.2171	1.5541	3.1614	< 0.001

CONCLUSION

In the network meta-analysis, there was no significant difference among tocilizumab, abatacept, and rituximab in achieving an ACR70. Based on the result of multivariate meta-regressions, if the conditions of the RCTs were similar, we estimate that abatacept could increase the chance of reaching an ACR70 response by 2.2-fold compared to tocilizumab.

KEYWORDS

Rheumatoid arthritis, Network meta-analysis, Rituximab, Tocilizumab, Abatacept.