Infections and Gastrointestinal Side Effects in the Rheumatoid Arthritis Comparison of Active Therapies Trial

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Introduction

- Few blinded trials have compared conventional DMARD therapy to newer biologics in the treatment of rheumatoid arthritis (RA) for methotrexate partial responders.
- The RA Comparison of Active Therapies Trial (RACAT) found that first triple therapy (T), with sulfasalazine and hydroxychloroquine added to methotrexate, was noninferior to first starting etanercept (E) plus methotrexate (NEJM 2013;369:307-18)
- Comparing side effects of T and E would provide information to help clinicians make a decision on prescribing these two therapies given that their clinical effectiveness were found to be similar in the RACAT trial

Study Aim

- To examine differences between the T strategy and the E strategy in the most common adverse events reported in RACAT, gastrointestinal (GI) toxicity and infections

Methods

Trial Design

- Double blinded trial with 48-week intervention
- 353 methotrexate suboptimal-responders were randomized to T (N=178) or E (N=175).
- Patients without significant improvement in Disease Activity Score for 28-joint counts (DAS28 < 1.2) were switched to the alternate treatment (E or T) at 24 weeks

Data

- Serious (SAE) or non-serious (NAE) infectious and GI adverse events reported during the intervention period and for 4 weeks after completing the intervention among 4 subgroups: 134 patients with T only, 44 patients T switched to E, 131 patients E only, and 44 patients E switched to T
- 8 switcher patients had infection events occurred both when they were receiving T and when they were receiving E. Only the infection events that occurred when receiving T were included in the analysis
- 5 switcher patients had GI events occurred both when they were receiving T and when they were receiving E. Only the GI events that occurred when receiving E were included in the analysis.

Statistical Analysis

- Chi-Square test and t-test were used for categorical variables and continuous variables respectively to compare treatments on patient characteristics
- Logistic and linear regression was used to compare treatments on SAEs and NAEs, controlling for age, gender, race, BMI, cigarette smoking, and comorbidity

Results

Table 1: Patient Characteristics by Treatment

	T (n=134)	T switched to E (n=44)	E switched to T (n=44)	E (n=131)
Male (%)	58.2	52.3	54.5	49.6
Caucasian (%)	88.8	95.5	81.8	85.4
Age [mean (SD)]	58.1 (12.8)	57.0 (13.7)	58.6 (12.5)	55.0 (13.4)
BMI m/kg2 [mean (SD)]	30.0 (5.9)	29.8 (6.2)	29.8 (6.4)	29.5 (6.9)
Cigarette Smoking (%)				
Never Smoked	35.8	20.5	31.8	35.1
Former Smoker	39.6	50	43.2	38.2
Current smoker	24.6	29.5	25	26.7
Comorbidity (%)				
No Comorbidity	18.7	29.5	18.2	26.7
Having one comorbidity	38.8	27.3	36.4	33.6
Having at least two comorbidities	42.5	43.2	45.5	39.7

There were no significant differences among the treatment groups on patient characteristics.

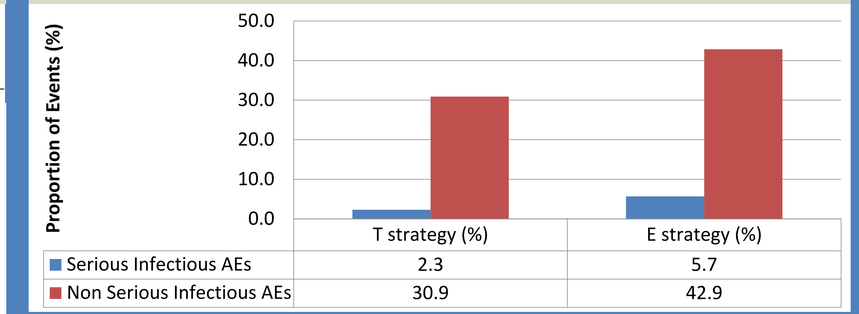
Table 2: Serious Infectious Adverse Event by Treatment

Names of Infections	Current treatment at the time of SAE		
	T	E	Total
Pneumonia	2	6	8
Oral/Nasopharygeal	0	2	2
Bronchitis	0	1	1
Renal and Genito-Urinary	0	1	1
Soft tissue	0	1	1
Viral infection	0	1	1
Clostridium difficile colitis	1	0	1
Diverticulitis	1	0	1
Total	**4**	**12**	**16**

Table 3: Serious Gastrointestinal Adverse Events by Treatment

Names of GI	Current treatment at the time of SAE		
	T	E	Total
Bowel obstruction	1	0	1
Gastritis	2	0	2
Gastrointestinal hemorrhage	0	3	3
Ileus	1	0	1
Pancreatitis	1	1	2
Total	**5**	**4**	**9**

Figure: Infectious Adverse Events by Treatment



Key Findings

- Participants who were on E were more likely to have infectious NAEs (adjusted OR= 1.6, p=0.03) and had a higher total number of events than participants who were on T (adjusted mean of 0.7 vs. 0.4, p <0.01).
- Though numbers of SAE were small, there was a trend toward a greater likelihood of infectious SAEs (adjusted OR=2.8, p=0.09) and a greater number of infectious SAEs that occurred when receiving E than T (12 vs. 4, p=0.18)
- Pneumonia was the most common infectious SAEs for both treatments (6 E and 2 T).
- GI NAEs were significantly more frequent in T vs. E (adjusted mean of 0.4 vs. 0.2, p=0.03)
- The amount of time on treatment when the GI events occurred was shorter for T than E (mean duration 10.0 vs. 17.7 weeks, p=0.001).

Conclusions

Infections were more likely to occur and occurred in greater numbers when patients were receiving Etanercept. On the other hand, GI symptoms were significantly more frequent in Triple Therapy and occurred earlier in the course of therapy. Our study findings might help clinicians when prescribing medications by considering patients' tolerance of each treatment's more common adverse events.

Supported by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development, Canadian Institutes for Health Research and NIH-ARRA by interagency agreements. Placebo etanercept donated by Amgen.