ANTI-TNF-α INHIBITORS IN PREVENTING ALZHEIMER'S DISEASE (AD): A RETROSPECTIVE REVIEW USING BOTH EMR AND CLAIMS DATA

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OBJECTIVES

It is widely believed that inflammation contributes to the pathogenesis of Alzheimer's Disease (AD).[1] More recently, the immunosuppressant drug etanercept has been implicated in reducing the risk of AD.[2] Confirmatory research is warranted to determine the role etanercept and its entire anti-TNF-α drug class has in preventing AD, which is the 6th leading cause of death in the US and its prevalence on the rise with an increasing aging population.[3] Therefore, TNF-α inhibitors are surmised to be of potential benefit for preventing AD and are further explored in retrospective study.

METHODS

Patients were identified as either receiving an anti-TNF-α drug (etanercept, adalimumab, certolizumab, infliximab, or golimumab) or anti-TNF-α naïve receiving methotrexate (MTX) as the control arm. Patient cohorts were generated in both an electronic medical records (EMR) research network of 55M patient lives and a 202M patient network of linked primary care data with medical and pharmacy claims. Neither cohort had AD (ICD-10: G30) prior to the 'anytime' outcome window. The risk of AD from 1 year after first exposure to either anti-TNF-α or MTX was analyzed using measures of association and survival analysis conducted via Kaplan-Meier estimator. Both sets of cohort comparisons were also run with propensity score matching (PSM) to control for demographic, comorbidity, medication, and diagnostic procedure confounders. [Table 1]

Table 1. Baseline cohort characteristics

	Data Networks							
	Before PSM Matching				After PSM Matching			
	EMR Cohorts		Claims Cohorts		EMR Cohorts		Claims Cohorts	
	Anti-TNF-α	MTX	Anti-TNF-α	MTX	Anti-TNF-α	MTX	Anti-TNF-α	MTX
Mean age (SD)	50.9 (18.4)	57.1 (20.2)	54.3 (16.8)	61.3 (18.1)	54 (17.4)	53.9 (20.7)	57.4 (15.9)	57.1 (19.3)
Not Hispanic or Latino	76.47%	73.47%	29.54%	27.50%	74.68%	74.73%	27.94%	28.58%
White	76.46%	72.13%	27.81%	24.90%	74.66%	74.42%	25.85%	26.42%
Female	61.05%	67.63%	62.57%	70.35%	64.29%	64.57%	67.15%	66.52%
Male	38.19%	31.68%	37.40%	29.63%	34.89%	34.63%	32.82%	33.46%
Unknown race	12.38%	12.55%	69.20%	71.43%	12.98%	12.82%	70.92%	70.25%
Black or African American	9.18%	13.00%	2.33%	3.04%	10.21%	10.62%	2.59%	2.66%
Hispanic or Latino	6.54%	6.95%	2.84%	3.06%	6.68%	6.68%	2.92%	2.97%
Asian	1.46%	1.71%	0.39%	0.37%	1.60%	1.57%	0.38%	0.40%
Factors influencing health status and contact with health services	57.15%	58.60%	50.27%	52.71%	54.05%	55.96%	50.06%	50.25%
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	53.20%	56.81%	44.75%	48.40%	50.96%	52.90%	44.94%	44.93%
Diseases of the musculoskeletal system and connective tissue	51.09%	53.75%	45.68%	51.68%	49.80%	51.23%	46.95%	47.31%
Diseases of the digestive system	42.64%	33.68%	33.98%	28.71%	35.16%	36.78%	30.22%	30.09%
Endocrine, nutritional and metabolic diseases	34.83%	39.23%	32.32%	37.97%	34.71%	36.07%	33.55%	33.68%
Diseases of the circulatory system	28.28%	37.83%	25.98%	34.26%	30.96%	32.46%	28.47%	28.65%
Diseases of the skin and subcutaneous tissue	31.64%	29.53%	27.10%	25.49%	29.69%	30.71%	25.86%	25.90%
Diseases of the nervous system	28.33%	33.35%	24.59%	28.82%	29.00%	30.14%	25.67%	25.78%
Diseases of the respiratory system	27.56%	32.15%	26.46%	29.59%	28.26%	29.48%	27.14%	27.14%
Diseases of the genitourinary system	24.86%	29.57%	22.05%	26.62%	25.94%	27.01%	23.66%	23.85%
Neoplasms	17.83%	28.43%	13.67%	18.25%	21.39%	23.03%	15.78%	15.70%
Evaluation and management services	58.36%	61.16%	54.12%	55.49%	55.69%	57.33%	53.42%	53.50%
Surgery	48.83%	49.99%	45.40%	47.60%	45.48%	47.06%	45.29%	45.31%
Pathology and laboratory procedures	46.35%	48.19%	51.54%	53.14%	43.70%	45.12%	50.98%	51.08%
Medicine services and procedures	42.23%	47.30%	42.50%	46.47%	41.98%	43.34%	43.42%	43.24%
Radiology procedures	43.62%	46.64%	43.44%	47.54%	41.72%	43.28%	44.28%	44.35%
Central nervous system medications	50.71%	54.25%	46.56%	62.10%	48.67%	50.40%	50.57%	50.08%
Hormones / synthetics / modifiers	50.73%	53.00%	47.56%	64.24%	47.61%	49.50%	51.57%	50.65%
Dermatological agents	46.80%	49.30%	41.76%	53.34%	44.50%	46.26%	44.70%	44.34%
Gastrointestinal medications	44.20%	45.55%	34.64%	43.56%	40.88%	42.67%	36.21%	35.87%
Ophthalmic agents	40.46%	44.27%	37.50%	49.72%	39.02%	40.70%	40.44%	40.06%
Cardiovascular medications	37.40%	44.97%	32.18%	51.48%	38.25%	39.89%	36.61%	36.02%
Nasal and throat agents, topical	38.53%	42.02%	31.17%	40.41%	37.18%	38.84%	33.39%	33.20%
Antimicrobials	37.22%	41.75%	40.87%	55.23%	36.60%	38.11%	44.38%	44.04%
Respiratory tract medications	35.55%	39.24%	28.42%	37.99%	34.47%	36.02%	30.47%	30.38%
Musculoskeletal medications	35.54%	38.90%	33.73%	47.28%	34.45%	35.88%	36.43%	36.62%
Therapeutic nutrients / minerals / electrolytes	30.78%	34.74%	17.56%	22.52%	29.97%	31.35%	18.50%	18.29%
Genitourinary medications	28.65%	31.00%	21.64%	28.81%	27.64%	28.93%	23.27%	23.16%
Vitamins	32.09%	25.78%	23.23%	25.77%	24.85%	26.48%	20.74%	20.82%
Antihistamines	22.19%	26.93%	15.59%	22.12%	23.02%	24.19%	17.15%	17.21%
Pharmaceutical aids / reagents	22.43%	26.63%	8.96%	10.28%	22.68%	23.83%	9.39%	9.23%
Irrigation / dialysis	22.21%	26.23%	9.06%	10.31%	22.42%	23.57%	9.46%	9.29%
Blood products / modifiers / volume expanders	18.53%	27.13%	8.50%	15.35%	21.07%	22.26%	10.17%	10.34%
Autonomic medications	16.57%	18.85%	9.96%	11.91%	16.48%	17.28%	10.39%	10.31%
Antineoplastics	22.64%	11.78%	21.49%	6.84%	12.94%	14.11%	12.67%	11.84%
Immunological agents	14.45%	13.33%	12.25%	14.56%	13.08%	13.70%	12.84%	13.03%

RESULTS

There was significant AD prevention with anti-TNF-α treatment compared to MTX found in both EMR (RR 1.824, p= <0.0001) and claims data networks (RR 2.370, p= <0.0001) before PSM. [Table 2] Significant results were also yielded in EMR (RR 1.310, p= <0.0001) and claims data networks (RR 1.501, p= <0.0001) with PSM applied. [Table 3] Time to AD outcome was measured up to 5,500 days in the EMR cohort with survival probability 98.577% for anti-TNF-α and 97.095% for MTX (p= <0.0001). In the claims cohorts, survival probability was 97.214% for anti-TNF-α and 94.640% for MTX (p= <0.0001) also measured across 5,500 days post index. Similar significant survival findings (p= <0.0001) were seen in both the EMR and claims comparisons that used PSM. [Figures 1-4]

Table 2. Cohort comparisons before / after PSM matching

	Data Networks							
	Before PSM Matching				After PSM Matching			
	EMR Cohorts		Claims Cohorts		EMR Cohorts		Claims Cohorts	
	Anti-TNF-α	MTX	Anti-TNF-α	MTX	Anti-TNF-α	MTX	Anti-TNF-α	MTX
# of pts	124,846	142,080	836,983	972,146	92,202	92,142	547,030	546,603
# pts w/outcome	199	413	2,826	7,780	178	233	2,305	3,457
Risk	0.159%	0.291%	0.338%	0.800%	0.193%	0.253%	0.421%	0.632%
RD	0.131%		0.463%		0.060%		0.211%	
p =	< 0.0001		< 0.0001		0.0065		< 0.0001	
RR	1.824		2.370		1.310		1.501	
95% CI	(1.540, 2.159)		(2.271, 2.474)		(1.078, 1.592)		(1.424, 1.582)	
Survival probability	98.577%	97.095%	97.214%	94.640%	98.322%	97.946%	96.46%	95.692%
Days after index	5,500		5,500		5,500		5,500	
p =	< 0.0001		< 0.0001		< 0.0001		< 0.0001	

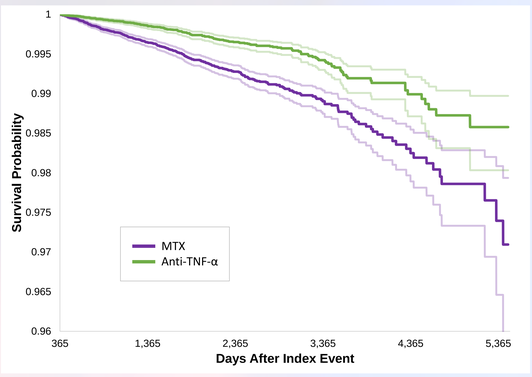

Figure 1. EMR cohorts Kaplan-Meier analysis before PSM

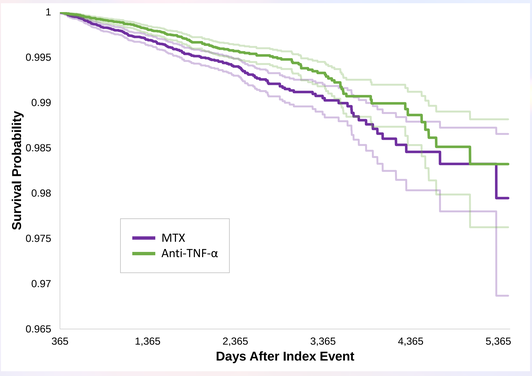

Figure 2. EMR cohorts Kaplan-Meier analysis after PSM

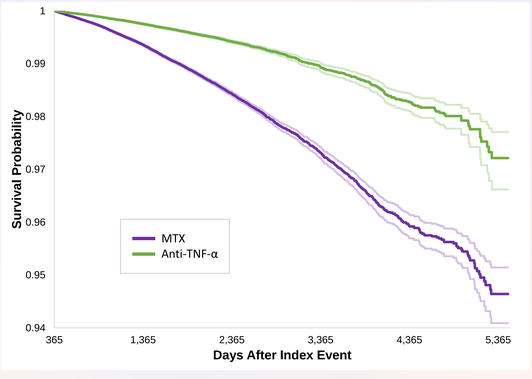

Figure 3. Claims cohorts Kaplan-Meier analysis before PSM

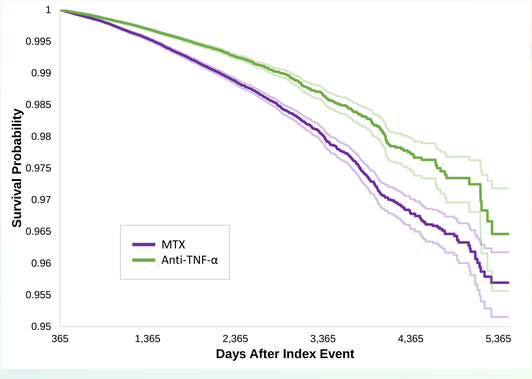

Figure 4. Claims cohorts Kaplan-Meier analysis after PSM

CONCLUSIONS

This study provides RWD-based evidence that points to anti-TNF-α therapies as a beneficial treatment in the prevention of AD. These findings are validated in two distinct types of data, EMR and claims, and significance is still evident with PSM applied to both analyses. Further research is warranted to investigate these results in even larger cohorts and with the AD outcome to be monitored in a longer outcome window. Additionally, the effect of TNF-α inhibitors should be explored in other inflammation-related CNS diseases such as multiple sclerosis and the broad "umbrella" diagnosis of dementia in which AD falls within.

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