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Initiation of anti-TNF therapy and the risk of optic neuritis; from the Safety Assessment of Biologic ThERapy (SABER) Study

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Abstract

Objective/Purpose—Optic neuritis (ON) cases have been reported in patients using anti-tumor necrosis factor (TNF) alpha therapy. However, no population-based studies have been conducted to assess the risk of this complication associated with anti-TNF drugs.

Design—Cohort study

Participants—New users of anti-TNF therapy (etanercept, infliximab, or adalimumab) or non-biologic disease modifying agents (DMARDs) during 2000–2007 from the following data sources: Kaiser Permanente Northern California, Pharmaceutical Assistance Contract for the Elderly, Tennessee Medicaid, and National Medicaid/Medicare.

Methods—We used validated algorithms to identify ON cases occurring after onset of new drug exposure. We calculated and compared ON rates between exposure groups.

Main outcome measures—ON incidence rates by medication exposure group

Results—We identified 61,227 eligible inflammatory disease patients with either new anti-TNF or new non-biologic DMARD use. Among this cohort, we found three ON cases among anti-TNF new users, occuring a median 123 days (range, 37–221 days) after anti- TNF start. The crude incidence rate of ON across all disease indications among anti-TNF new users was 10.4 (95% CI 3.3–32.2) cases per 100,000 person-years. In a sensitivity analysis considering current or past anti-TNF or DMARD use, we identified a total of 6 ON cases; 3 among anti-TNF users and 3 among DMARD users. Crude ON rates were similar among anti-TNF and DMARD groups, 4.5 (95% CI 1.4–13.8) and 5.4 (95% CI 1.7–16.6) per 100,000 person-years, respectively.

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Potential conflicts:
Other authors no conflicts

Conclusion—Optic neuritis is rare among those who initiate anti-TNF therapy and occurs with similar frequency among those with non-biologic DMARD exposure.

Keywords

shingles; zoster; herpes; biologic therapy; tumor necrosis factor-alpha; rheumatoid arthritis; adverse events; psoriasis

Background

Optic neuritis (ON) is a heterogeneous condition with a number of potential etiologies including infectious, auto-immune, toxic, demyelinating, and other causes. The incidence of ON is not well-established, nor is the proportion of ON caused by various etiologies well-documented. Modern estimates of disease rates are lacking, but population-based data from Minnesota in the late 1980's suggest idiopathic ON (i.e. no identifiable cause) occurs at a rate of 5/100,000 (1). More recently, certain biologic immunosuppressive therapies have been linked to triggering acute demyelinating ON. These therapies inhibit tumor necrosis factor-alpha (TNF) and are now widely employed against rheumatoid arthritis, inflammatory bowel disease, psoriasis, and other inflammatory conditions including non-infectious uveitis. Case reports of patients developing ON during anti-TNF use exist (2), although to date, no formal, analytic studies have been conducted to explore the rate of this presumed complication, and no studies have evaluated whether these therapies actually elevate the risk of this complication.

To evaluate the association of ON and anti-TNF therapy, we first reviewed all spontaneous ON reports from the National Registry of Drug Induced Ocular Side Effects (Casey Eye Institute, Portland, Oregon). We then proceeded to evaluate this possible association in the context of a large collaboration called "SAfetyof Biologic ThERapy (SABER)" in which the rate of ON could be calculated and compared between patients starting biologic disease modifying drugs (DMARDs) (i.e. anti-TNF therapy) to similar patients starting non-biologic DMARDs (e.g. methotrexate, others).

Methods

National Registry of Drug Induced Ocular Side Effects (NRDIOSE)

The NRDIOSE (Casey Eye Institute, Portland, Oregon) passively collects reports of ocular toxic drug events from physicians within the United States and abroad (3). In addition, the registry is linked with the FDA Medwatch system (Rockville, Maryland) and the WHO's Spontaneous Event Reporting Systems (Uppsala, Sweden) such that events reported to all three systems are retrievable within the NRDIOSE. To search the NRDIOSE to identify anti-TNF associated cases of ON reported bewteen 1/1/1999 to 9/22/2011, we used the following search terms: "optic neuritis," "optic neuropathy," "etanercept," "infliximab," "adalimumab," "golimumab," "certolizumab," and "tumor necrosis factor alpha antagonist." For each reported case, we extracted descriptive data with regard to timing of ON onset after drug start, resolution of ON after drug cessation, patient demographics, and outcome information where reported. These reports generally contained very little clinical information making validation of ON cases not possible.

SABER data sources and cohort formation

We utilized data from four large US automated databases from 1998 through 2007 to conduct a cohort study: 1) National Medicaid and Medicare databases (Medicaid Analytic eXtract, 2000–2005; Medicare, 2000–2006; and Medicare Part D, 2006); 2) Tennessee Medicaid (TennCare, 1998–2005); 3) The New Jersey's Pharmaceutical Assistance to the Aged and Disabled, and the Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PAAD/PACE, 1998–2006); and, 4) Kaiser Permanente Northern California (KPNC, 1998–2007). We used validated algorithms to identify patients with immune-mediate inflammatory diseases of interest (rheumatoid arthritis, psoriasis, ankylosing spondylitis, and inflammatory bowel disease) (4),(5). Patients were eligible for inclusion if they had a baseline period of 365 days with continuous enrollment in the respective database preceding the first biologic or non-biologic DMARD prescription fill. Patients with ICD-9 codes for HIV, organ transplant, diagnoses for ≥2 autoimmune diseases, or history of ON given prior to first DMARD prescription fill (T_0) were excluded. Among potential cohort members, we identified new users of study DMARDs, (6) defined as having filled a prescription for a study DMARD after 365 baseline days without prescriptions filled for the specific study medication or others in the same group. Study DMARDs were classified in two groups: TNF-α antagonists (including infliximab, adalimumab and etanercept) and alternate DMARD regimens. For RA, the alternate regimens were initiation of leflunomide, sulfasalazine or hydroxychloroquine after use of methotrexate in the previous year ("methotrexate failures"). For IBD the comparison group was initiation of azathioprine or 6-mercaptopurine (AZA/6-MP), whereas for PsO-PsA-AS the comparison was initiation of non-biologic DMARDs (including methotrexate, hydroxychloroquine, sulfasalazine and leflunomide). Follow-up continued through the earliest of the following dates: death, loss of enrollment, development of ON, switch to another DMARD regimen or the discontinuation of the current regimen (defined as 30 days without medication), or study end, whichever came first. Patients who left the cohort could subsequently contribute new episodes of medication use if selection criteria were re-fulfilled. Patients could contribute episodes to more than one exposure group. A detailed description of SABER data development has been reported elsewhere (7).

Because exposure to these therapies could potentially increase the long term risk of ON even after discontinuation, a secondary analysis (termed analysis of "current and past users ") was conducted in which new users were considered exposed during drug use and for up to 365 days after drug discontinuation with such exposure censored at time of death, ON development, or a start of alternative DMARD regimen if any of these occurred earlier than 365 days after drug discontinuation.

ON case-finding

To identify ON cases, we used a combination of ICD-9 codes for ON and lab tests (e.g. RPR, serum ACE level, Orbital MRI, others) typically ordered during an acute ON work-up. We identified ON cases using the following algorithm: any patient given one inpatient or outpatient ICD-9 code for ON (377.30 or 377.32) with evidence of serum ACE testing within 90 days of the code OR any patient given an ON ICD-9 code three times within 60 days. Prior to its use, we determined that this case-finding algorithm had a positive

predictive value (PPV) of 100% by conducting a manual review of all cases with ≥1 ON diagnostic codes (n= 135) during 2008 at OHSU and the Portland Veteran's Administration Medical Center in Portland, Oregon.

Because the above case-finding algorithms were of high PPV but potentially lacked sensitivity, as part of additional sensitivity analysis, we constructed ON case-finding algorithms that were less stringent. For this analysis, we defined ON as a physician given inpatient or outpatient ICD-9 code (377.30 or 377.32) given > 2 times within 90 days.

Covariates

Covariates measured within the baseline period prior to drug start included demographics: age, gender, race, residence (urban/rural), nursing home/community dwelling, area income, calendar year; generic markers of comorbidity: number of hospitalizations, outpatient and emergency room visits, number of different medication classes filled; surrogate markers of inflammatory disease severity: extra-articular disease manifestations, number of intra-articular and orthopedic procedures, number of laboratory tests ordered for inflammatory markers, use of corticosteroids (8)(9)(10)(11)(12).

Analysis

We calculated crude incidence rates of ON by underlying disease group (RA, IBD, PsO-PsA-AS) as well as by first DMARD exposure (new biologic users versus non-biologic DMARD failure). We compared crude incidence rates between treatment groups. All analyses were done in SAS. This study was approved by the IRBs of all SABER participating institutions

Results

National Registry of Drug Induced Ocular Side Effects

From the national registry collecting passively reported data, we identified 358 reports of ON occurring in association with anti-TNF therapy. Seventy-five percent were female, median age 44 years (range, 6–78 years), with median time between anti-TNF start and diagnosis of 182 days (range, 2–388 days). Cases were most numerous with etanercept (n=169), with fewer reported with monoclonal antibodies infliximab (n=122), adalimumab (n=55), golimumab or certolizumab (n=5), or multiple drugs (n=7). Rechallenge (n=5) and dechallenge (n=33) information was available for very few reported cases. One of five patients rechallenged with drug had recurrent symptoms, whereas 13 of 33 patients stopping drug had continued symptoms despite drug stoppage.

SABER cohort study

Within SABER, we identified 61,227 eligible inflammatory disease patients with either new anti-TNF or new non-biologic DMARD use (Figure 1). Baseline characteristics between those treated with anti-TNF therapy and those in comparison non-biologic groups were similar within all disease cohorts (Table 1 for RA cohort, on-line tables 1–2).

Primary analysis ("current user" analysis)

In the primary current user analysis, we identified three ON cases in 28,898 person-years of exposure among anti-TNF new users with RA (N=2) or IBD (n=1), occurring a median of 123 days (range, 37–221 days) after anti-TNF start. These three cases occurred in females, median age 60 years (range 40–65 years), with exposure to infliximab (n=2) and etanercept (n=1). No case occurred in 15,799 person-years of exposure within the non-biologic DMARD comparison group. The crude incidence rate of ON across all disease indications among anti-TNF new users was 10.4 (95% CI 3.3–32.2) cases per 100,000 person-years (Table 2).

Secondary analysis ("current and past user" analysis)

In our secondary analysis ("current and past users"), we identified 3 additional ON cases, all 3 within the non-biologic DMARD group. Crude ON rates were similar among anti-TNF and comparison groups, 4.5 (95% CI 1.4–13.8) and 5.4 (95% CI 1.7–16.6) cases per 100,000 person-years, respectively. (Table 2)

Sensitivity analyses using alternate ON case definition

Using the alternative and presumably more sensitive case-finding algorithm (ICD-9 code given ≥ 2 times in 90 days), within our "current user" analysis, we identified 3 ON cases among anti-TNF new users (n=2 among RA patients, and n=1 in IBD) and one ON case among non-biologic DMARD users (Table 3). The three anti-TNF associated cases (infliximab, n=3) occurred median 221 days (37, 651 days) after anti-TNF drug start. Crude incidence rates of ON across all disease indications among anti-TNF new users were 10.4 (3.4–32.2) cases per 100,000 person-years, and 6.3 (0.9, 44.9) cases per 100,000 person-years for new DMARD users. In our current and past user analysis with the potentially more sensitive case definition, we detected a larger number of cases including 10 nonbiologic DMARD cases (RA =5, IBD =1, PsO/PsA/AS = 4) and seven anti-TNF associated cases (RA=5, IBD = 2). These seven anti-TNF associated cases (infliximab n=6, etanercept n=1 occurred median 311 days (range, 37 – 1650 days) after drug start, and 5 were females of median age 50 (range, 25 – 85 years). Comparison of rates within disease indications, as well as across disease indications, yielded similar incidence estimates for ON in biologic and non-biologic DMARD exposure groups.

Discussion

Within SABER, a large US multi-institutional research initiative, we performed the first large cohort study specifically examining ON incidence in patients starting biologic therapy with anti-TNF agents. We found the incidence of ON to be low in this group, approximately 5–10 per 100,000 patient-years, and comparable to published rates from other studies estimating the incidence of ON. Most importantly, our secondary analyses and sensitivity analyses suggest ON rates to be similar in patients who started anti-TNF therapies compared to similarly diseased patients who started non-biologic immunosuppressive therapies.

Our findings suggest that anti-TNF therapy initiation might not promote the development of ON in patients who lack a documented history of this condition. We excluded anyone with a

history of ON in the 12 months prior to study entry, so we cannot comment as to whether such therapy could exacerbate already pre-existing demyelinating disease. Early studies of anti-TNF therapy (specifically lenercept, a p55 TNF receitor fusion protein attached to an IgG1 molecule) in patients with active multiple sclerosis (MS) documented an increase in MS flares for MS patients treated with anti-TNF therapy (13). While this phenomenon is not well-understood, it has been hypothesized that TNF could be important in the clearance of disease causing auto-immune T cells within existing demyelinating lesions, such that TNF blockade could exacerbate such disease (14). As for patients without a known history of underlying demyelinating disease, a mechanism by which anti-TNF therapy could promote such lesions has not been well-articulated or understood.

Our findings stand in contrast to the large number of spontaneous adverse event reports of ON occurring in patients using anti-TNF therapy. A total of 17 such patients have been reported in the scientific literature and a total of 358 such reports are contained within our passive surveillance database within the Casey Eye Institute that collects adverse ocular events from WHO, FDA, and physician sources (3)(2). Little clinical information is contained within these reports making their verification not possible, and the proportion of individuals who had underlying MS or other demyelinating conditions prior to anti-TNF therapy is not known. While most of these spontaneous reports were in association with etanercept, we found a majority of cases within SABER in association with infliximab, particularly in our larger current and past user analysis. We believe our study highlights the shortcomings of such voluntary, spontaneous report databases for monitoring drug safety. While passive surveillance can provide important information with regard to adverse events, particularly with regard to hypothesis generation, such databases do not collect denominator data, and the rates and relative risks of such complications cannot be calculated.

Our cohort study has certain strengths and limitations. First, our patient cohorts were large allowing for evaluation of rare events, and our methods allowed us to focus on those presumably at highest risk for ON, new users of anti-TNF or non-biologic therapies. Exclusion of prevalent users in our primary analysis importantly avoids the potential for survivor bias that can minimize the magnitude of increased risk that could be associated with a drug exposure of interest (6). In addition, we performed several sensitivity analyses in which patients were considered exposed for up to one year after drug-discontinuation (until new drug exposure, death, or development of ON) and this produced no difference in our relative incidence findings between exposure groups. Further, in analyses using a presumably more sensitive (and less specific) case-finding algorithms for ON, we found higher disease rates in all groups, but again, found no difference in disease rates based upon new drug exposure. However, our study also has some important limitations. First, while we found that our ON case-finding algorithms had high PPV locally (the VA and OHSU patient systems were used for this exercise prior to conducting the SABER study), the predictive value of these algorithms in different healthcare systems used to conduct SABER is not known. Further, the sensitivity of these algorithms is not known, and we were not able to review medical records to verify cases of ON identified within our study. Not withstanding, the range of incidence estimates of ON identified within our study are in line with estimates reported by prior population-based studies of ON.

Our findings should be reassuring to ophthalmologists and other clinicians wishing to start anti-TNF therapy in patients with inflammatory diseases. While we are limited in making conclusions regarding the use of this therapy in patients with pre-existing demyelinating disease, randomized control trial and other data suggest that use of anti-TNF therapy in such patients might worsen underlying demyelinating disease. Until further studies are conducted in such patients, those patients who develop demyelinating disease during anti-TNF therapy should avoid such therapy in the future. Future pharmacovigilance studies using similar methods could be valuable in examining other reported ocular-toxic drug events for which population-based data are lacking.

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Table 1

Baseline characteristics of inflammatory disease cohorts by exposure group.

Variables	Rheumatoid Arthritis N (%)		Inflammatory Bowel Disease N (%)		Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis N (%)	
	Anti-TNF	Non-biologic DMARD	Anti-TNF	Non-biologic DMARD	Anti-TNF	Non-biologic DMARD
Age, mean (SD), year	57.73 (14.53)	58.47 (14.27)	40.39 (16.13)	40.38 (17.80)	48.82 (15.33)	52.19 (16.82)
Female	20955 (85.9)	10205 (86.3)	2559 (66.5)	4330 (63.1)	2854 (56.1)	4331(61.4)
Race						
White	15244 (62.5)	7340 (62.0)	3010 (78.2)	5075 (73.9)	3716 (73.0)	4986 (70.7)
Black	3927 (16.1)	1831 (15.5)	586 (15.2)	993 (14.5)	357 (7.0)	576 (8.2)
Other	5212 (21.4)	2659 (22.5)	254 (6.6)	799 (11.6)	1017 (20.0)	1489 (21.1)
Nursing home resident during baseline	992 (4.1)	493 (4.2)	99 (2.6)	167 (2.4)	146 (2.9)	334 (4.7)
≥1 hospitalization during baseline	6995 (28.7)	3305 (27.9)	2133 (55.4)	3387 (49.3)	1042 (20.5)	1613 (22.9)
Charlson-Deyo Comorbidity score[1], mean (SD)	1.72 (1.13)	1.73 (1.17)	0.51 (0.95)	0.47 (0.90)	0.74 (1.13)	0.79 (1.18)
≥1 Inflammatory Marker tested	8955 (36.7)	4380 (37.0)	1094 (28.4)	2058 (30.0)	1045 (20.5)	1370 (19.4)
Mean glucocorticoid use, prednisone equivalents						
None	9732 (39.9)	5079 (42.9)	1714 (44.5)	2773 (40.4)	4038 (79.3)	5461 (77.5)
(0–5 mg)	7552 (31.0)	3650 (30.9)	609 (15.8)	973 (14.2)	700 (13.8)	1162 (16.5)
(10 mg-high)	2495 (10.2)	1056 (8.9)	933 (24.2)	1954 (28.5)	156 (3.1)	153 (2.2)
(5–10 mg)	4604 (18.9)	2045 (17.3)	594 (15.4)	1167 (17.0)	196 (3.9)	275 (3.9)
Any orthopedic surgery	1752 (7.2)	633 (5.4)	66 (1.7)	85 (1.2)	189 (3.7)	177 (2.5)
Any intra-articular injection	8607 (35.3)	3596 (30.4)	198 (5.1)	259 (3.8)	695 (13.7)	817 (11.6)
Comorbidites						
COPD	3241 (13.3)	1584 (13.4)	311 (8.1)	484 (7.0)	502 (9.9)	870 (12.3)
Cerebrovascular disease	947 (3.9)	419 (3.5)	82 (2.1)	118 (1.7)	116 (2.3)	248 (3.5)
Diabetes	4618 (18.9)	2266 (19.2)	336 (8.7)	541 (7.9)	1021 (20.1)	1337 (19.0)

Variables	Rheumatoid Arthritis N (%)		Inflammatory Bowel Disease N (%)		Psoriasis, Psoriatic Arthritis, Ankylosing Spondylitis N (%)	
	Anti-TNF	Non-biologic DMARD	Anti-TNF	Non-biologic DMARD	Anti-TNF	Non-biologic DMARD
Obesity	2153 (8.8)	1227 (10.4)	276 (7.2)	676 (9.8)	697 (13.7)	953 (13.5)
Medication initiated						
Adalimumab	5888 (24.1)	-	118 (3.1)	-	294 (5.8)	-
Etanercept	10283 (42.2)	-	-	-	4270 (83.9)	-
Infliximab	8212 (33.7)	-	3732 (96.9)	-	526 (10.3)	-
Hydroxychloroquine	-	5730 (48.4)	-	-	-	569 (8.1)
Leflunomide		4569 (38.6)				133 (1.9)
Sulfasalazine	-	1531 (12.9)	-	-	-	858 (12.2)
Mercaptopurine	-			3475 (50.6)	-	
Methotrexate	-	-	-		-	5491 (77.9)
Azathioprine	-	-	-	3392 (49.4)		-

Table 2

Crude incidence of optic neuritis in patients who initiate anti-TNF or non-biologic DMARD therapy by inflammatory disease indication

	Current User Analysis		Current and Past User Analysis	
	Person-Years	**Rate* (per 100,000 person-years)**	**Person-Years**	**Rate+ (per 100,000 person-years)**
RA				
Methotrexate failures	7227	0	23758	8.4 (2.1, 33.7)
Anti–TNF new users	22461	8.9 (2.2, 35.6)	51339	3.9 (1.0, 15.6)
IBD				
AZA/6MP	4608	0	14510	0
Anti –TNF new users	2319	43 (6.1, 306)	7439	13.4 (1.9,95.4)
PsO, PsA, AS				
Non biologic DMARD	4119	0	17710	5.6 (0.8,40.1)
Anti–TNF new users	3963	0	8620	0
Across all indications				
Non biologic DMARD	15954	0	55,979	5.4 (1.7,16.6)
Anti–TNF new users	28743	10.4 (3.3, 32.2)	67,399	4.5 (1.4,13.8)

*"Current user" analysis in which exposure stops at drug stop

+"Current and past user" analysis in which exposure continues for 365 days after drug start until new exposure occurs TNF = tumor necrosis factor; DMARD=disease-modifying anti rheumatic drug; AZA=azathioprine; 6MP=6 mercaptopurine

Note: rules associated with use of Medicare data preclude including case numbers within tables when cell values are less than 11.

Table 3

In sensitivity analysis (use of more sensitive optic neuritis case-finding algorithms): crude incidence of optic neuritis in patients who initiate anti-TNF or non-biologic DMARD therapy by inflammatory disease indication

	Current User Analysis		Current and Past User Analysis	
	Person-Years	**Rate* (per 100,000 person-years)**	**Person-Years**	**Rate+ (per 100,000 person-years)**
Rheumatoid arthritis				
Non biologic DMARD	0	0	23750	21.1 (8.8, 50.6)
Anti-TNF new users	22461	8.9 (2.2, 35.6)	51334	9.7 (4.1, 23.6)
IBD				
AZA/6MP	4608	0	14509	6.9 (1.0, 48.9)
Anti-TNF new users	2319	43 (6.1, 306)	7437	26.9 (6.7, 107.5)
PsO, PsA, AS				
Non biologic DMARD	4119	0	17706	22.6 (8.5,60.2)
Anti-TNF new users	3963	0	8620	0
Across all indications				
Non- biologic DMARD	15799	6.3 (0.9, 44.9)	55964	17.9 (9.6, 33.2)
Anti-TNF new users	28743	10.4 (3.4,32.2)	67392	10.4 (4.9, 21.8)

*"Current user" analysis in which exposure stops at drug stop

+"Current and past user" analysis in which exposure continues for 365 days after drug start until new exposure occurs TNF = tumor necrosis factor; DMARD=disease-modifying anti rheumatic drug; AZA=azathioprine; 6MP=6 mercaptopurine

Note: rules associated with use of Medicare data preclude including case numbers within tables when cell values are less than 11