

RISK OF DEMYELINATING EVENTS IN PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING TUMOUR NECROSIS FACTOR INHIBITORS: A SYSTEMATIC LITERATURE REVIEW

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BACKGROUND

- Several case reports published in the 2000's indicated that demyelinating diseases could be a serious adverse event following TNF inhibitors (TNFi).
- However, initial data from biological therapy registries did not bring enough clarification.

OBJECTIVES

To investigate whether treatment with biologics or targeted synthetic DMARDs is associated with an increased risk of demyelinating events among patients with rheumatoid arthritis (RA)

METHODS

A systematic search was performed in MEDLINE, EMBASE (up to October 2022), and by manual references lists with the selection criteria:

- **POPULATION** = patients with RA
 - **INTERVENTION** = treatment with any biologic including TNFi and targeted synthetic DMARDs,
 - **OUTCOME** = demyelinating event
 - **STUDY DESIGN** = observational studies & RCT.
- Titles and abstracts were screened and data were extracted from the selected studies including quality evaluation, and outcomes of interest.

Table: Characteristics and incidence rates of demyelinating events in the included studies in chronological order

Study	Design	Population	Outcome
Lingyi 2022 (1)	Nested case-control Canadian healthcare databases	N= 462/296,918 Rheumatic diseases, mixed population	Case = multiple sclerosis Pooled IRR (95% CI): 2.05 (1.13-3.72)
Taylor 2021 (2)	Prospective Cohort British Society for Rheumatology Biologics Register	N= 35/13,489 Mixed population of inflammatory arthritis	Incidence (95% CI): 19.7/100,000 pts-years (13.7-27.3) SIR (95% CI): 1.38 (0.96-1.92) Definite cases: 0.83 (0.51-1.26) Males: 2.75 (1.31-5.06)
Kunchok 2020 (3)	Nested case-control Medical records at Mayo Clinic (USA)	N=106 cases/106 controls Autoimmune diseases	Case = Any inflammatory CNS event OR 4.82 (95%CI 1.62-14.36)
Koop 2020 (4)	Combined biologic registers in Sweden and Denmark	N=271 and 51/111,455 RA pts	Incidence Rate: 0.37-0.39/1000 pt-yrs HR (95% CI) TNFi exposed vs non: Sweden: 0.97 (0.72 to 1.33) Denmark: 1.45 (0.74 to 2.81)
Dreyer 2016 (5)	Register-based cohort study DANBIO	N= 27,880 patients with arthritis and TNFi therapy	SIR 1.11 (95% CI 0.63-1.93) RA: 0.65 (95% CI 0.24-1.72) Males: 3.48 (95% CI 1.45-8.37)
Fernandez-Espartero 2011 (6)	BIOBADASER-Spain	N= 9/13,075 RA pts-years	Incident rate in RA: 0.69 (95% CI: 0.36-1.32) MS 0.05 (95% CI: 0.01-0.33), vs Spanish population 0.02-0.04*1000
Bernatsky 2010 (7)	Nested case-control Administrative data in Canada	N= 104,958 RA pts 81 cases and 810 controls	Adjusted rate ratios (95% CI): TNFi 1.31 (0.68 - 2.50) Anakinra 0.80 (0.29 - 2.24) MTX 1.09 (0.63 - 1.89)

Abbreviations: RA, rheumatoid arthritis; SIR, standardized incidence rate; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; OR, odds ratio; MTX, methotrexate; MS, multiple sclerosis; TNFi, tumour necrosis factor inhibitor.

References: 1. Li L, et al *Neurology*. 2022 Oct 28;10.1212. 2. Taylor TRP, et al. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(3). 3. Kunchok A, et al *JAMA Neurol*. 2020;77(8):937-46. 4. Kopp TI, et al. *Ann Rheum Dis*. 2020;79(5):566-72. 5. Dreyer L, et al. *Ann Rheum Dis*. 2016;75(4):785-6. 6. Fernandez-Espartero MC, et al. *Semin Arthritis Rheum*. 2011;41(3):524-33. 7. Bernatsky S, et al. *Ann Rheum Dis*. 2010;69(9):1691-3.

RESULTS

- From 368 identified studies, 4 cohorts and 3 nested case-control studies reported risk of demyelinating events in patients with inflammatory arthritis following treatment with biologics, mainly TNFi and anakinra, in one study.
- Most studies included mixed populations of RA and other inflammatory arthritis and patients with RA were analysed as a separate subgroup in some of the studies.
- Two nested case-control reported an increased risk but included a population of autoimmune diseases, with no analysis of a subgroup of patients with RA. In general, demyelinating events were very uncommon in patients receiving TNFi, with a marginal increased risk in males with RA in two studies (Table).

CONCLUSIONS

- No consistent and significant risk of demyelinating disease following TNFi treatment was found in patients with RA.
- Only a marginal and slight increase of risk was found in male patients with RA.
- The small number of events in these registries is reassuring when considering TNFi.
- A careful consideration is recommended in individuals at highest risk or with family history of demyelinating diseases.