CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

# Risk of Venous Thromboembolism in Patients with Rheumatoid Arthritis: Initiating Disease-Modifying Antirheumatic Drugs

Seoyoung C. Kim, MD, MSCE, ScD,[a,b,c] Daniel H. Solomon, MD, MPH,[a,b] Jun Liu, MD, MPH,[a] Jessica M. Franklin, PhD,[a] Robert J. Glynn, ScD, PhD,[a] Sebastian Schneeweiss, MD, ScD[a,c]

[a]*Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, Mass;* [b]*Division of Rheumatology, Allergy and Immunology, Brigham and Women's Hospital, Boston, Mass;* [c]*Department of Epidemiology, Harvard School of Public Health, Boston, Mass.*

## ABSTRACT

**OBJECTIVES:** Recent research suggests that rheumatoid arthritis increases the risk of venous thromboembolism. This study compared the risk of venous thromboembolism in patients with newly diagnosed rheumatoid arthritis initiating a biologic disease-modifying antirheumatic drug (DMARD) with those initiating methotrexate or a nonbiologic DMARD.

**METHODS:** We conducted a population-based cohort study using US insurance claims data (2001-2012). Three mutually exclusive, hierarchical DMARD groups were used: (1) a biologic DMARD with and without nonbiologic DMARDs; (2) methotrexate without a biologic DMARD; or (3) nonbiologic DMARDs without a biologic DMARD or methotrexate. We calculated the incidence rates of venous thromboembolism. Cox proportional hazard models stratified by propensity score (PS) deciles after asymmetric PS trimming were used for 3 pairwise comparisons, controlling for potential confounders at baseline.

**RESULTS:** We identified 29,481 patients with rheumatoid arthritis with 39,647 treatment episodes. From the pairwise comparison after asymmetric PS trimming, the incidence rate of hospitalization for venous thromboembolism per 1000 person-years was 5.5 in biologic DMARD initiators versus 4.4 in nonbiologic DMARD initiators and 4.8 in biologic DMARD initiators versus 3.5 in methotrexate initiators. The PS decile-stratified hazard ratio of venous thromboembolism associated with biologic DMARDs was 1.83 (95% confidence interval [CI], 0.91-3.66) versus nonbiologic DMARDs and 1.39 (95% CI, 0.73-2.63) versus methotrexate. The hazard ratio of venous thromboembolism in biologic DMARD initiators was the highest in the first 180 days versus nonbiologic DMARD initiators (2.48; 95% CI, 1.14-5.39) or methotrexate initiators (1.80; 95% CI, 0.90-3.62).

**CONCLUSIONS:** The absolute risk for venous thromboembolism was low in patients with newly diagnosed rheumatoid arthritis. Initiation of a biologic DMARD seems to be associated with an increased short-term risk of hospitalization for venous thromboembolism compared with initiation of a nonbiologic DMARD or methotrexate.

 • *The American Journal of Medicine (2015) 128, 539.e7-539.e17*

**KEYWORDS:** Disease-modifying antirheumatic drugs; Rheumatoid arthritis; Venous thromboembolism

Several studies recently showed that patients with rheumatoid arthritis have a 1.5 to 6 times increased risk of venous thromboembolism, including pulmonary embolism and deep vein thrombosis.[1-5] It is thought that active systemic inflammation may lead to the development of venous thromboembolism because inflammatory cytokines such as interleukin-6, interleukin-8, and tumor necrosis factor (TNF)-α activate coagulation pathways and thus alter thrombotic tendency.[6,7] To date, limited evidence is available on whether treatment of rheumatoid arthritis with any

**Funding:** See last page of article.
**Conflict of Interest:** See last page of article.
**Authorship:** See last page of article.
Requests for reprints should be addressed to Seoyoung C. Kim, MD, ScD, MSCE, 1620 Tremont St, Suite 3030, Boston MA 02120.
E-mail address: skim62@partners.org

0002-9343/$ -see front matter 
http://dx.doi.org/10.1016/j.amjmed.2014.11.025

disease-modifying antirheumatic drugs (DMARDs) or a specific type of DMARD, such as biologic DMARDs including TNF-α inhibitors, increases or decreases the risk of venous thromboembolism. Although several studies report cases of venous thromboembolism or peripheral thrombosis after treatment with TNF-α inhibitors for rheumatoid arthritis or other inflammatory diseases,[8-12] a few small studies found that TNF-α blockade with infliximab in patients with rheumatoid arthritis decreases inflammatory and coagulation markers and reduces the inhibition of fibrinolysis.[13,14] Furthermore, a cohort study based on the British Society for Rheumatology Biologics Register (BSRBR) showed no significant association between TNF-α inhibitors and venous thromboembolism in patients with rheumatoid arthritis.[15]

**CLINICAL SIGNIFICANCE**

- Initiation of a biologic disease-modifying antirheumatic drug (DMARD) seems to be associated with an increased short-term risk of hospitalization for venous thromboembolism compared with initiation of a nonbiologic DMARD or methotrexate.
- The absolute risk of hospitalization for venous thromboembolism was low in patients with rheumatoid arthritis initiating biologic DMARDs or nonbiologic DMARDs.

On the basis of the potential link between DMARD treatment and thrombosis, we examined the risk of incident venous thromboembolism in patients with newly diagnosed rheumatoid arthritis initiating a biologic DMARD, methotrexate, or other nonbiologic DMARDs. In addition, we investigated both short- and long-term risks of venous thromboembolism associated with the use of specific DMARD treatment.

## PATIENTS AND METHODS

### Data Source

We conducted a cohort study using the claims data from 3 commercial US health plans (2001-2012)—WellPoint, United HealthCare, and Aetna—which insure primarily working adults and their family members across the United States. These databases contain longitudinal claims information, including medical diagnoses, procedures, hospitalizations, physician visits, and pharmacy dispensing. Personal identifiers were removed from the dataset before the analysis to protect subject confidentiality. Therefore, patient informed consent was not required. The study protocol was approved by the Institutional Review Board of Brigham and Women's Hospital.

### Study Cohort

Adults aged 18 years or more with at least 2 visits, which were 7 to 365 days apart, coded with the International Classification of Diseases, 9th Revision, Clinical Modification code 714.xx, for rheumatoid arthritis, were identified. To identify patients with newly diagnosed rheumatoid arthritis, patients were required to have a minimum of 12 months of continuous insurance eligibility before the first rheumatoid arthritis diagnosis and to be free of any DMARD dispensing any time before their first rheumatoid arthritis diagnosis. Patients were also required to have less than 365 days between the first rheumatoid arthritis diagnosis and the first DMARD dispensing. Subjects with malignancies, prior venous thromboembolism, or dispensing for an anticoagulant any time before their index date were excluded (**Supplementary Table 1**, available online).

### Disease-Modifying Antirheumatic Drug Exposures

We defined 3 mutually exclusive, hierarchical groups of DMARDs: (1) a biologic DMARD with and without methotrexate or other nonbiologic DMARDs; (2) methotrexate with and without other nonbiologic DMARDs; or (3) 1 or more nonbiologic DMARDs other than methotrexate (**Supplementary Table 2**, available online). Subjects in the methotrexate group could not simultaneously use a biologic DMARD; however, they could use other nonbiologic DMARDs (eg, triple therapy). The nonbiologic DMARD group could not simultaneously use a biologic DMARD or methotrexate, but they could start more than 1 other nonbiologic DMARD at the index date (eg, concurrent use of hydroxychloroquine and leflunomide). The date of initiating a DMARD in 1 of these 3 exposure groups was defined as the start of follow-up (ie, index date). Patients were also allowed to cross-over to a different DMARD category at their first switching. Therefore, all the included patients in this study were required to have had at least 2 rheumatoid arthritis diagnoses and at least 1 filled prescription for a DMARD at the start of follow-up. A previous validation study showed that patients with rheumatoid arthritis can be identified accurately using a combination of diagnosis codes for rheumatoid arthritis and DMARD prescriptions in claims data with a positive predictive value greater than 86%.[16]

For a given DMARD category, patients were followed up until discontinuing the drug or switching to a different DMARD category (ie, "as treated" analysis), the occurrence of venous thromboembolism, the loss of health plan eligibility, the end of study period, or death. In the case of drug discontinuation, the exposure risk window for each patient treatment episode extended until 30 days after the expiration of the supply of the last fill. Patients were allowed to enter the study cohort up to 2 times.

### Outcome Definition

We defined the venous thromboembolism event as a hospitalization for venous thromboembolism, either deep vein