Risk Factors for Thromboembolic Events Among Patients With Immune-mediated Diseases

Yarur A,[1] Mu F,[2] Setyawan J,[3] Zichlin ML,[2] Yang H,[2] Fernan C,[2] Billmyer E,[2] Downes N,[2] Azimi N,[4] Strand V[5]

[1]Division of Gastroenterology and Hepatology, Medical College of Wisconsin, Milwaukee, WI, US; [2]Analysis Group Inc., Boston, MA, US; [3]Arena Pharmaceuticals, San Diego, CA, US; [4]Sharp Grossmont Hospital, La Mesa, CA, US; [5]Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, CA, US

P1461

BACKGROUND

- Immune-mediated diseases (IMD) are linked to an increased risk of thromboembolic events
  - Thromboembolic events include venous events such as deep vein thrombosis (DVT) and pulmonary embolism (PE), and arterial events such as ischemic stroke (IS) and myocardial infarction (MI)
  - Prior literature has identified the following as known risk factors for thromboembolic events: history of a thromboembolic event, obesity, diabetes, and cardiovascular disease[1,2,3]
- Recent novel agents to treat IMD, such as janus kinase (JAK) inhibitors, have been introduced and their impact on thromboembolic events is still unclear
  - There have been reports suggesting a potential link between venous thromboembolic events and JAK inhibitors, but no study has been done in IMD patients[4-6]
- Given the burden of thromboembolic events, it is important to understand the risk of thromboembolic events associated with IMD, and whether the use of associated treatments or the presence of certain comorbidities further impacts such risk
  - To our knowledge, this is the first systematic and comprehensive assessment of the risk factor profiles (i.e., clinical risk factors & treatments) in an IMD population that are potentially linked to thromboembolic events

OBJECTIVE

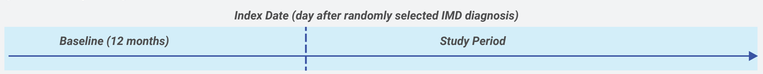
- To evaluate the risk factor profile for thromboembolic events among patients with IMD
  - Thromboembolic events included DVT, PE, IS, and MI
  - IMD included ankylosing spondylitis, atopic dermatitis, inflammatory bowel disease, multiple sclerosis, plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, and systemic lupus erythematosus

METHODS

DATA SOURCE

- This was a retrospective study of IBM MarketScan® Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits Databases: 2014-2018
  - These databases include both employer-paid (e.g., active employees, early retirees, Consolidated Omnibus Budget Reconciliation Act [COBRA] continues, and dependents) and employer-sponsored Medicare supplemental healthcare encounters
  - Data contain enrollment history, dates of service, claims for medical (e.g., professional and institutional services) and pharmacy services, and some demographic variables (e.g., age, sex, and geographic region)

Figure 1. Study Design



Index Date

- The index date was defined as the day after a randomly selected date of a medical claim with an IMD diagnosis to capture patients at different points in their disease spectrum, i.e., with different severities and treatment profiles; if the first IMD diagnosis was chosen, then the sample would be a group of predominantly newly diagnosed patients

Baseline

- The baseline period was defined as the 12-month period prior to the index date

Study Period

- The study period was defined as the time from the index date until the earliest of patient death, end of continuous eligibility, or end of data
- Patients were required to have at least 30 days of continuous eligibility following the index date, and were followed for up to four years

BASELINE

- The following characteristics were assessed during the baseline period:
  - Demographics (e.g., age at index date, sex)
  - Index year
  - History of thromboembolic events
  - Clinical conditions of interest (e.g., comorbidities, pregnancy)
  - Common classes of drug use (e.g., hormone replacement therapy, oral contraceptives, glucocorticoids, biologics, etc.)

STATISTICAL ANALYSIS

- To evaluate risk factors for thromboembolic events among patients with IMD, prediction models were conducted separately for each outcome (i.e. number of DVT, PE, IS, and MI events during the study period)
  - Incidence rate ratios (IRRs) and p-values were estimated using generalized linear models with a Poisson distribution and a sandwich (robust) variance estimator
    - An offset was used to account for varying lengths of follow-up time
  - All baseline characteristics were assessed in the risk factor profiles
- *P*-values <0.05 were considered statistically significant

RESULTS

Figure 2. Sample Selection of Patients With IMD

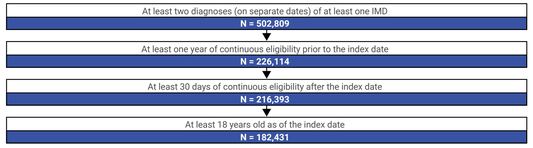


Table 1. Demographics and Clinical Characteristics of IMD Patients During the Baseline Period

Characteristic	IMD (N = 182,431)
Age at index date (years)	
Mean ± SD	51.3 ± 15.5
Sex (female), n (%)	117,337 (64.3%)
Index year	
2015	46,877 (25.7%)
2016	49,466 (27.1%)
2017	43,429 (23.8%)
2018	42,659 (23.4%)
History of thromboembolic events, n (%)	7,431 (4.1%)
Deep vein thrombosis	3,150 (1.7%)
Ischemic stroke	2,568 (1.4%)
Pulmonary embolism	1,479 (0.8%)
Myocardial infarction	1,411 (0.8%)
Conditions of interest, n (%)	
Cancer	15,575 (8.5%)
Cardiovascular diseases	93,006 (51.0%)
Atherosclerosis	14,017 (7.7%)
Atrial fibrillation	5,931 (3.3%)
Heart failure	5,128 (2.8%)
Hyperlipidemia	63,270 (34.7%)
Hypertension	68,853 (37.7%)
Chronic kidney disease	7,093 (3.9%)
Chronic obstructive pulmonary disease	9,165 (5.0%)
Diabetes	
Type 1	2,877 (1.6%)
Type 2	24,407 (13.4%)
Fracture (hip or leg)	1,356 (0.7%)
Peripheral vascular disease	9,197 (5.0%)
Pregnancy[1]	3,565 (3.0%)
Common classes of drug use, n (%)	
Non-IMD drugs	
Hormone replacement therapies[1]	9,051 (7.7%)
Testosterone replacement therapies[1]	1,916 (2.9%)
Oral contraceptives[1]	12,394 (10.6%)
IMD drugs	
Biologics	23,019 (12.6%)
TNF inhibitors	17,965 (9.8%)
Interferon beta-1a	1,337 (0.7%)
Interleukin inhibitors	3,477 (1.9%)
Other biologics	1,221 (0.7%)
Glucocorticoids	67,269 (36.9%)
JAK inhibitors	930 (0.5%)
Non-biologic immunomodulators	50,009 (27.4%)
Methotrexate	21,199 (11.6%)
S1P-receptor modulators	970 (0.5%)
Other non-biologic immunomodulators	34,326 (18.8%)
NSAIDs	51,724 (28.4%)
5-aminosalicyclic-acid derivative agents	20,416 (11.2%)

Abbreviations:
IMD, immune-mediated disease; JAK, Janus kinase; NSAID, nonsteroidal anti-inflammatory drugs; S1P, sphingosine-1-phosphate; SD, standard deviation; TNF, tumor necrosis factor
Notes:
[1]The proportions of patients with pregnancy, hormone replacement therapies, and oral contraceptives were reported out of the total number of females in each group. The proportion of patients with testosterone replacement therapies was reported out of the total number of males in each group.

Table 2. Risk Factor Profiles for Thromboembolic Events Among Patients With IMD

	Deep vein thrombosis IRR[1]	Pulmonary embolism IRR[1]	Ischemic stroke IRR[1]	Myocardial infarction IRR[1]
Immune-mediated disease				
Ankylosing spondylitis	1.02	0.73	0.68	0.86
Atopic dermatitis	0.76	0.68	0.72	0.93
Inflammatory bowel disease	1.33*	1.30	0.79	0.84
Multiple sclerosis	1.20	1.40	1.37	0.90
Psoriasis	0.85	0.86	0.74	1.11
Psoriatic arthritis	0.90	1.05	0.83	1.46
Rheumatoid arthritis	1.04	1.08	0.72*	1.18
Systemic lupus erythematosus	1.61**	1.60**	1.44*	1.35
Baseline thromboembolic event[2]	41.10***	112.31***	22.70***	13.58***
Demographics				
Sex (female)	0.88*	0.84	1.00	0.69***
Age at index date	1.02***	1.02***	1.05***	1.05***
Comorbidities				
Cancer	1.37***	1.19	1.07	0.72**
Cardiovascular diseases	1.26**	1.28*	1.53**	2.60***
Chronic kidney disease	1.15	0.90	1.26	1.45**
Chronic obstructive pulmonary disease	1.04	0.96	1.06	1.19
Type 1 diabetes	1.04	0.77	1.13	1.68**
Type 2 diabetes	1.08	1.09	1.54***	1.30*
Fracture	1.10	0.74	1.08	0.82
Peripheral vascular disease	1.07	0.89	1.24*	1.54***
Pregnancy	1.22	0.90	1.01	0.64
Common classes of drug use				
Non-IMD drugs				
Hormone replacement therapies	0.64**	0.61*	0.56***	0.84
Testosterone replacement therapies	0.70	1.43	1.73	0.58*
Oral contraceptives	1.40*	0.83	1.54	0.47
IMD drugs				
Biologics				
TNF inhibitors	1.12	1.18	1.12	0.98
Interferon beta-1a	1.26	2.16	0.89	1.52
Interleukin inhibitors	0.76	1.68	0.69	1.32
Other biologics	1.80*	1.73	1.39	0.85
Glucocorticoids	1.20**	1.19*	0.99	1.21*
JAK inhibitors	1.23	2.52*	1.82	0.76
Non-biologic immunomodulators				
Methotrexate	0.97	1.06	0.90	1.15
S1P-receptor modulators	0.61	0.30	0.33*	0.54
Other non-biologic immunomodulators	1.03	1.01	0.82*	0.82
NSAIDs	0.93	0.98	0.94	0.93
5-aminosalicylic-acid derivative agents	1.08	0.88	0.75*	1.08

Abbreviations:
IMD, immune-mediated disease; IRR, incidence rate ratio
Notes:
[1]Significance stars: *P<0.05, **P<0.01, ***P<0.001
[2]Baseline deep vein thrombosis, baseline pulmonary embolism, baseline ischemic stroke, and baseline myocardial infarction are controlled for in the deep vein thrombosis, pulmonary embolism, ischemic stroke, and myocardial infarction models, respectively.

SUMMARY

Patient Characteristics

- The cohort (N=182,431) had an average age of 51.3 years and was predominantly female (64.3%) (see **Figure 2** and **Table 1**)
- Patients had the following types of IMD, in order of prevalence: rheumatoid arthritis (25.9%), psoriasis (24.9%), inflammatory bowel disease (19.0%), atopic dermatitis (14.8%), systemic lupus erythematosus (7.7%), multiple sclerosis (7.4%), psoriatic arthritis (5.2%), and ankylosing spondylitis (2.3%) **(data on file)**
- Overall, 4.1% of IMD patients had a history of thromboembolic events during the baseline period (see **Table 1**)
- The IMD patients experienced extensive comorbidities during the baseline period; 51.0% had cardiovascular disease, including 34.7% with hyperlipidemia and 37.7% with hypertension (see **Table 1**)
- The most common prescription medications taken by IMD patients were glucocorticoids (36.9%), NSAIDs (28.4%), non-biologic immunomodulators (27.4%), and biologics (12.6%) (see **Table 1**)

Risk factor profiles

- Risk factor profiles varied by type of thromboembolic event, but the largest consistent risk factor was history of thromboembolic event during baseline period (IRRs: DVT 41.10; PE 112.31; IS 22.70; MI 13.58; p<0.001 for all) (see **Table 2**)
- Comorbidities, such as cardiovascular disease (CVD), type 2 diabetes, and peripheral vascular disease were associated with increased rates of MI (2.60, 1.30, 1.54, respectively; p<0.05 for all) and IS (1.53, 1.54, 1.24, respectively; all p<0.05) (see **Table 2**)
  - CVD was also associated with increased rates of DVT (1.26, p<0.01) and PE (1.28; p<0.05) (see **Table 2**)
- Use of glucocorticoids was associated with increased rates of DVT (1.20, p<0.01), PE (1.19, p<0.05), and MI (1.21, p<0.05), but not IS (0.99; NS) (see **Table 2**)
- Use of JAK inhibitors were associated with an increased rate of PE (2.52; p<0.05) and numerically increased rates of DVT (1.23; NS) and IS (1.82; NS) (see **Table 2**)
- Use of S1P-receptor modulators was associated with decreased rates for all types of thromboembolic events, with significant findings for IS (DVT: 0.61; NS; PE: 0.30, NS; IS: 0.33, p<0.05; MI: 0.54, NS) (see **Table 2**)

LIMITATIONS

- Limitations inherent to retrospective observational studies using claims data:
  - Administrative claims data only contain diagnostic and procedure codes recorded for reimbursement purposes and may be subject to coding errors or data omissions
  - Patients may not have used the recorded medication as prescribed after filling a prescription
- Several known clinical predictors of thromboembolic events (e.g., smoking status, obesity) are not captured in insurance claims dataset and could not be assessed as part of the risk factor profile
- As the data cut spans 2014-2018, this analysis provides an early look into recently approved treatments for IMD (e.g., JAK inhibitors, S1P-receptor modulators). Confirmatory studies including a larger sample of patients using newer treatments for IMD are warranted. As the market uptake of these treatments increases, there will be a larger public health impact since more people will be exposed to the therapies

CONCLUSIONS

- Several factors were found to have an additional impact on the rate of thromboembolic events. These risk factors included previous thromboembolic event, comorbidities, and classes of medications
- Some treatments were found to potentially increase the risk (e.g., glucocorticoids, JAK inhibitors), whereas others were found to possibly mitigate the risk (e.g., S1P-receptor modulators)
- Further studies are warranted to validate these risk factors among patients with IMD
- The associated risk factors of thromboembolic events among patients with IMD should be carefully considered when optimizing treatment for patients with IMD with the aim to balance risks and benefits of the chosen therapy

Presented at American College of Gastroenterology (ACG)
October 23–28, 2020 • Virtual

REFERENCES: **1.** Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular Risk Factors and Venous Thromboembolism Incidence: The Longitudinal Investigation of Thromboembolism Etiology. *Arch Intern Med*. 2002;162(10):1182–1189. doi:10.1001/archinte.162.10.1182. **2.** Wattanakit K, Lutsey PL, Bell EJ, et al. Association between cardiovascular disease risk factors and occurrence of venous thromboembolism. A time-dependent analysis. *Thromb Haemost*. 2012;108(3):508-515. doi:10.1160/TH11-10-0726. **3.** Libertiny G, Hands L. Deep venous thrombosis in peripheral vascular disease. *Br J Surg*. 1999;86(7):907-910. doi:10.1046/j.1365-2168.1999.01129.x. **4.** Scott, L.C., Hider, S.L. and Scott, D.L., 2018. Thromboembolism with Janus kinase (JAK) inhibitors for rheumatoid arthritis: how real is the risk?. *Drug Safety*, 41(7), pp.645-653. **5.** U.S. Food and Drug Administration (2019). FDA approves Boxed Warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR). Accessed September, 2020. **6.** Verden A, Dimbil M, Kyle R, Overstreet B, Hoffman KB. Analysis of Spontaneous Postmarket Case Reports Submitted to the FDA Regarding Thromboembolic Adverse Events and JAK Inhibitors. *Drug Saf*. 2018;41(4):357-361.

ACKNOWLEDGMENTS AND DISCLOSURES: **AY** has received consulting fees from Takeda, Prometheus Bioscience and Arena Pharmaceuticals. **FM, MLZ, HY, CF, EB,** and **ND** are employees of Analysis Group, which received consultancy fees from Arena Pharmaceuticals to conduct this analysis. **JS** is an employee of Arena Pharmaceuticals. **NA** served as a speaker and advisor for Daiichi Sankyo, Janssen, Gilead, a speaker for Astra Zeneca, and was a member of the Delphi panel for Arena Pharmaceuticals. **VS** has received consultancy fees from Abbvie, Amgen Corporation, Arena, Astra Zeneca, Bayer, BMS, Boehringer Ingelheim, Celltrion, Crescendo, Galapagos, Genentech / Roche, Gilead, GSK, Ichnos, Inmedix, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Samsung, Sandoz, Sanofi, Servier, Setpoint, UCB.