Examining the Link between Autoimmune Disease and Thromboembolic Events: A Modified Delphi Panel Approach

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INTRODUCTION

- In the United States, the estimated prevalence of immune-mediated diseases (IMD) is 5 to 8% of population[1] and IMDs are the third leading cause of illness and mortality.[2]
- Individuals with an IMD have a higher risk of developing thromboembolic events (TEs).[3]
- While studies have suggested IMD as an independent risk factor for developing TEs, the potential relationship between IMD and TEs is largely impacted by patient factors (e.g., age and sex), medical histories,[4, 5] as well as treatment options.[6]
- While there is a growing body of evidence connecting TEs in patients with an IMD, physician understanding and awareness of this relationship varies.
- Consequently, a multidisciplinary panel of physicians was convened utilizing a modified Delphi approach, to gain understanding on the relationship between TEs and IMDs.
- The primary objective of the panel was to assess areas of consensus regarding the IMDs most prone to TE as well as modifiable and unmodifiable factors that might exacerbate the risk of TEs.

METHODS

- A modified version of the Delphi technique, a method for consensus building that uses an iterative approach, was conducted among a group of physicians with expertise across multiple disciplines.
- The modified Delphi panel consisted of four rounds of engagement based on IMD/TE relationships assessed from a rapid evidence literature review as background information prior to the panel (**Table 1**).
- The multidisciplinary panel was recruited from a list of 162 healthcare providers that was generated by identifying lead and senior author publications containing specific scientific keyword searches (“Venous Thromboembolism”, “VTE”, “Thromboembolic”, “JAK”, “TNF”, “S1P”) across 7 specialties: gastroenterology, neurology, rheumatology, cardiology, pulmonology, hematology/oncology, dermatology.

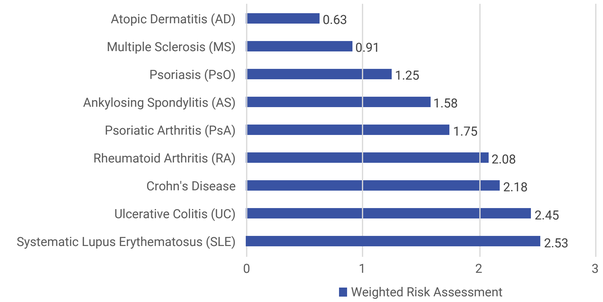
Table 1. Modified Delphi Design

Round of Engagement	Description
Semi-structured Interview	• Web-calls conducted to collect qualitative insights from each panel member. • Panel members were asked several open-ended questions including: (a) their experience with IMD patients; (b) their preferred treatment modalities; and (c) whether they thought IMD patients were at an increased risk of TE.
Pre-Meeting Questionnaire	• On-line questionnaire assessing panelist beliefs regarding the IMD patient population and risk of TEs and risk factors for TEs.
In-person Panel Discussion	• Large and small group discussion focused on the following topics: (a) IMDs most at risk for TEs; (b) modifiable and non-modifiable risk factors for TEs; (c) current therapies for IMDs; and (d) TE risk associated with IMD therapies.
Consensus Statement Questionnaire	• On-line questionnaire containing 13 proposed consensus statements (See Appendix C). • Panelists indicated the extent they agreed with each statement using a Likert-type scale ranging from “1” (Strongly Disagree) to “5” (Strongly Agree). • The consensus statements were based on the discussions during, and the themes that emerged from, the in-person panel meeting.

RESULTS

- 62% (8 of the 13) of panelists either agreed or strongly agreed (mean = 2.85; SD = .80) that all IMD patients were at a higher risk of TE compared to the general population.
- Systemic lupus erythematosus (SLE), ulcerative colitis (UC), Crohn’s Crohon’s disease, Rheumatoid arthritis (RA) had the highest risk of TE (**Figure 1**).

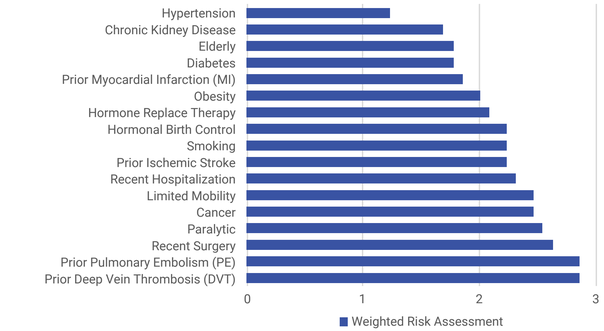
Figure 1. “For the following autoimmune disease patient populations, please indicate what you feel is the overall level of TE risk for the population as a whole” (n=13)



n=11 (AD, MS); n=12 (UC, CD, AS, PsA, PsO)
no risk=0; lower risk=1; moderate risk=2; high risk=3

- Patients that had a prior DVT or PE were considered at the greatest risk for another TE (**Figure 2**).

Figure 2. “For the following patient characteristics, please indicate your perceived level of TE risk for autoimmune disease patients” (n=13)



no risk=0; lower risk=1; moderate risk=2; high risk=3

MULTIDISCIPLINARY PANEL IN-PERSON MEETING

- **Figure 3** includes the key takeaways from the panel discussion of ulcerative colitis and Crohn’s Disease

Figure 3. Ulcerative Colitis & Crohn’s Disease: Characterizing High-Risk Patients and Altering Clinical Approach

Patient Characteristics That Cause an Alteration of Approach

- **Non-modifiable**
  - Prior clotting event
  - Primary sclerosing cholangitis
  - Age – 51 and over
  - Recent hospitalization
  - Smoking
  - Obesity
  - Immobility
  - Traum or lower-extremity surgery
  - Renal failure
  - Cancer
  - History of miscarriage
- **Modifiable**
  - Disease activity
  - Oral contraceptives
  - Hormone replacement therapy
  - Central lines

Approaches to Reduce TE Incidence in These Patients

- **Treatment**
  - Achieve remission as quickly as possible to reduce inflammation
  - Extend anti-coagulation therapy
  - Discontinue utilization of pro-coagulatory medications
- **Monitoring**
  - Increase visit frequency
  - Monitor for inflammation
  - Look at CRP as DA Marker
  - Perform thrombophilia panel in patients under 50
- **Patient Behaviors**
  - Avoid sedentary behavior
  - Quit smoking

Next Steps to Communicate

- **Raise TE Awareness in GI and PCP communities**
  - Characterize and stratify high-risk patients
  - Factor in autoimmune and inflammatory diseases in risk calculators
  - Establish and communicate low bleeding risk to reduce level of concern
- **Expand Anti-Coagulation Treatment**
  - Consider extending anti-coagulation in high-risk patients
  - Consider using VTE prophylaxis in high-risk in-patient/ambulatory patients
- **Treat Patients with More Advanced Treatments First-Line**
- **Encourage Preventative Measures and Proactive Monitoring**
  - Biomarkers, endoscopy

- JAKinibs and corticosteroids were identified as two therapeutic options that could benefit from closer examination in light of potential TE risk (**Figure 4**).

Figure 4. Treatment Modalities that Require Closer Evaluation in Light of TE Risk

JAKinibs

- There are potential concerns with increased TE risk in RA patients taking some JAKinibs
- There is not yet a universally accepted mechanism to explain this perceived increased risk
- Risk stratification tools are necessary for patients being considered for JAKinibs therapy
- Currently, JAKinibs play an important role for patients who have exhausted all other options
- Until more is learned about the TE safety signal, JAKinibs will likely remain predominantly reserved for the last line of therapy after all other advanced therapies in the treatment algorithm for patients with other risk factors for TEs
- Proper discussion of the benefits risk of JAKinibs with patients on oral contraceptives or hormone replacement therapy should be conducted

Corticosteroids

- Have become embedded in treatment algorithms and clinicians are familiar with the safety profile
- Corticosteroids should not be used longer than 2-3 months and the smallest dose possible should be utilized to achieved required effect
- Tapering of corticosteroids should be attempted and weaning of steroids to lowest possible dose should be attempted.

3.3.4 CONSENSUS STATEMENT QUESTIONNAIRE

- The results of the Consensus Statement Questionnaire are provided in **Table 2**.
  - 100% of the experts on the panel agreed that patients with an IMD are at a higher risk of TE compared to the general population, and certain classes of medications are associated with a higher risk of TE.
  - Most of the experts (93%) agreed that caution should be exercised when using certain classes of medications such as JAKinibs, but 100% said they would still use JAKinibs particularly in patients when other options have been exhausted (see Question 13 in **Table 1**).

Table 2. Results From Proposed Consensus Statement Questionnaire

Proposed Consensus Statement	N=12[a] Mean	SD	%Agreement (Agree or Slightly Agree)
Autoimmune Disease Patient Populations (Categorically Aggregated)	4.85		98.0%
1. Patients with autoimmune diseases are associated with a higher risk of thromboembolic events (TE) relative to the general population.	5	0	100.0%
2. Among patients with autoimmune diseases, patients with Lupus and Rheumatoid arthritis (RA) carry the highest risk of TE.	4.67	0.89	91.7%
3. Patients with inflammatory bowel diseases (Ulcerative Colitis [UC] or Crohn’s Disease [CD]) are associated with an increased risk of TE.	4.75	0.45	100.0%
4. Optimal management of patients with autoimmune diseases in these populations (Lupus/RA/IBD) should involve efforts to reduce the overall TE risk.	4.75	0.62	91.7%
5. In addition to the inherent risk of TEs in the autoimmune disease patient populations, there are additional risk factors that further increase TE risk – some modifiable and other non-modifiable.	5	0	100.0%
6. When patients with autoimmune diseases at risk for TEs carry non-modifiable an/or modifiable risk factors, the risk of TEs incrementally increases.	4.75	0.45	100.0%
7. The multidisciplinary physician community treating autoimmune disease patients should have increased awareness of TE risk, including the potential impact of modifiable and non-modifiable risk factors that further increase the risk of TE.	5	0	100.0%
Non-Modifiable Risk Factors			
8. Patients with autoimmune diseases at risk of TEs may have non-modifiable TE risk factors that further increase TE risk such as age, a prior clotting event, recent surgery or hospitalization, limited mobility, bleeding risk, and a history of miscarriage that should be considered when making treatment decisions.	5	0	100.0%
Modifiable Risk Factors: Categorically Aggregated →	4.82		98.0%
9. Physicians should encourage autoimmune disease patients to make lifestyle changes if they carry modifiable risk factors including smoking, obesity, and sedentary lifestyle.	5	0	100.0%
10. When considering treatment options for treating autoimmune disease patients at risk of TEs, physicians should assess all potential modifiable risk factors that may increase the risk of TEs, including medications.	4.83	0.39	100.0%
11. Certain classes of medications have been associated with increased risk of TEs including corticosteroids, oral contraceptives or hormone replacement therapy, and JAK inhibitors.	4.83	0.39	100.0%
12. Rheumatoid arthritis patients treated with tofacitinib 10 mg BID were observed to have an increased incidence of TEs.	4.83	0.39	100.0%
13. In order to minimize the risk of TEs in patients with autoimmune diseases, physicians should exercise caution when prescribing medications that have been associated with increased risk of TEs including corticosteroids, oral contraceptives or hormone replacement therapy, and JAK inhibitors.	4.75	0.87	92.7%
14. Despite a potential increase in TE risk, JAK inhibitors remain a viable option for autoimmune disease patients and have a role in treatment algorithms, especially amongst those who have exhausted other options.	5	0	100.0%
15. The use of tofacitinib may incrementally increase the risk of TEs in autoimmune disease patients that carry other TE risk factors including high BMI, sedentary lifestyle, and other medications such as corticosteroids, oral contraceptives or hormone replacement therapy.	4.67	0.65	91.7%
16. Based on the recent FDA and EMA approvals of the selective JAK-1 inhibitor, upadacitinib for the treatment of rheumatoid arthritis patients, the risk of TEs are viewed by regulatory authorities as a class-effect for all JAK inhibitors.	4.67	0.48	100.0%

[a] = One expert answered “strongly disagree” to every question.

DISCUSSION

- Patients with an IMD demonstrate an inherent higher risk of developing TE
- The panel of experts identified UC, Crohn’s disease, SLE, and RA as the top IMDs with the greatest risk of TE.
- Prior DVT and PE were both considered by most experts as characteristics that placed patients at a particularly high risk for TE.
  - JAKinibs and corticosteroids were two therapies that could benefit from additional research pertaining to their risk of TE.

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