Immunogenetics of infection and inflammation of the urogenital and gastrointestinal tracts and probiotics

Karimi, O.

2011

document version
Publisher's PDF, also known as Version of record

Chapter 6

JAK2 V617F Mutation Is Not Involved in Thromboembolism in IBD

Ouafae Karimi; J. Bart A. Crusius; Constantina Coucoutsi; Roel Heijmans; Alicia M. Sambuelli; A. Salvador Peña; Ioannis E. Koutroubakis

R1
R2
R3
R4
R5
R6
R7
R8
R9
R10
R11
R12
R13
R14
R15
R16
R17
R18
R19
R20
R21
R22
R23
R24
R25
R26
R27
R28
R29
R30
R31
R32
R33
R34
R35
R36
R37
R38
R39

To the Editor:

Recently Janus kinase 2 (*JAK2*) mutations have been described in several Philadelphia-negative myeloproliferative disorders (MDP) as polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis, conditions complicated by thrombosis.[1] The point mutation in *JAK2* encodes a valine-tophenylalanine change at position 617 (*JAK2* V617F) and confers constitutive tyrosine kinase activity.[2] It has been suggested that thrombosis in MPD may be due to *JAK2* mutation. Moreover, screening for *JAK2* V617F has been carried out in a series of splanchnic, cerebral, and leg deep vein thromboses (DVTs) without overt MDP.[3,4] Results from these studies indicate that the *JAK2* V617F mutation in the absence of overt MDP is highly associated with splanchnic vein thrombosis and sporadically with cerebral thrombosis. Thromboembolism is a diseasespecific extraintestinal manifestation of inflammatory bowel disease (IBD)5 that develops as the result of multiple interactions between acquired and genetic risk factors. Arterial and venous thromboembolism is the most important complication, representing a significant cause of morbidity and mortality in IBD patients. The most commonly detected risk factors for thrombophilia in this disease are factor V R506Q (Leiden) mutation, plasminogen activator inhibitor gene polymorphism, hyperhomocysteinemia, and antiphospholipid antibodies.

However, the prevalence of these factors does not differ between patients with IBD associated with vascular complications and those with thrombosis without IBD.[6]

Table 1. Clinical characteristics and *JAK2* V617F mutation status in IBD patients with vascular complications

Number of patients	48 (Crete 25; Argentina 23)
Ulcerative colitis	26 (Crete 15; Argentina11)
Crohn's disease	22 (Crete 10; Argentina12)
Median age onset of IBD	37.5 years
Female/male	16F/32M
Deep vein thrombosis of the leg	Crete 8UC/5CD; Argentina 9UC/8CD
Pulmonary emboli	2UC (Crete)
Retinal venous thrombosis	2CD (Argentina)
Splanchnic venous thrombosis	2UC (1 Crete; 1 Argentina)
Myocardial infarction	Crete 4UC/2CD; Argentina 2 CD
Ischemic stroke	Crete 2UC/1CD; Argentina 3CD
Presence of *JAK2* V617F mutation	0/48

Different cytokines stimulate the JAK and signal transducer and activator of transcription (JAK/STAT) pathway. JAK2 is also important in vascular diseases, such as atherosclerosis in which inflammation plays an important role.[7] The aim of our study was to investigate the frequency of the JAK2 V617F mutation, which is the most common mutation described in

MPD, in a group of 48 thrombotic IBD patients (22 with CD, 26 with UC) from Argentina (n =23) and Crete (n=25). The clinical characteristics of patients included in this study are reported in Table 1. No case had overt MPD, whereas some cases (n=4) had a history of more than 1 thrombotic event. The diagnosis of vascular complications was defined by typical clinical characteristics and diagnostic instrumental investigation (Doppler ultrasonography, computed tomography, magnetic resonance imaging, or angiography).

Genomic DNA was isolated from peripheral blood according to an inhouse DNAzol extraction procedure (Invitrogen, Breda, The Netherlands). Forty-eight patients with IBD varying in age of onset of IBD from 2 to 65 years (median 37.5 years) presented with different thrombotic events (Table 1). A semiquantitative Taqman assay was used to determine the percentage of the JAK2 V617F mutation among wild-type DNA. No JAK2 V617F mutation was found in the 48 IBD patients with thrombotic complications. JAK2 V617F mutation has been found associated with elevated hemoglobin levels and leukocytosis, which may be directly associated with the increased thrombotic risk in MPD. On the other hand, thromboembolism in IBD is not associated with elevated hemoglobin levels and leukocytosis. The finding of the absence of the JAK2 V617F mutation in the thrombotic IBD patients suggests that other mechanisms play an important role in the pathogenesis of thrombosis in IBD. The small number of cases with splanchnic vein thrombosis in our series (but also in other IBD series), which is mainly associated JAK2 V617F mutation, could also be an explanation of this finding. Because recent studies in MPD have found other mutations in the gene coding for JAK2 (chromosome 9p24) such as JAK2 exon 12 mutations,[8] further study of IBD patients with these serious complications is being undertaken.

References

1. Levine RL, Wadleigh M, Cools J, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell. 2005;7:387–397.
2. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med. 2003;348:1201–1214.
3. Boissinot M, Garand R, Hamidou M, et al. The JAK2–V617F mutation and essential thrombocythemia features in a subset of patients with refractory anemia with ring sideroblasts (RARS). Blood. 2006;108:1781–1782.
4. De Stefano V, Fiorini A, Rossi E, et al. Incidence of the JAK2 V617F mutation among patients with splanchnic or cerebral venous thrombosis and without overt chronic myeloproliferative disorders. J Thromb Haemost. 2007;5:708 –714.
5. Miehsler W, Reinisch W, Valic E, et al. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? Gut. 2004;53:542–548.
6. Koutroubakis IE, Sfiridaki A, Tsiolakidou G, et al. Genetic risk factors in patients with inflammatory bowel disease and vascular complications: case-control study. Inflamm Bowel Dis. 2007;13:410–415.
7. Burova E, Vassilenko K, Dorosh V, et al. Interferon gamma-dependent transactivation of epidermal growth factor receptor. FEBS Lett. 2007;581:1475–1480.
8. Rothlisberger B, Huber A, Bargetzi M, et al. JAK2 exon 12 mutation in JAK2V617F-negative polycythemia vera. Leuk Lymphoma. 2008;49:586 –588.