Diffuse alveolar hemorrhage associated with variant alleles increases the risk of pulmonary fibrosis in patients using oral anticoagulants

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Introduction

Diffuse alveolar damage (DAH) causes oxidative stress and inflammation in the lung. It has been suggested that oxidative damage plays a role in the pathophysiology of pulmonary fibrosis. Recently, we found that DAH was associated with vitamin K epoxide reductase (*VKORC1*) and cytochrome P450 (CYP) *2C9* variant alleles in patients using oral anticoagulation therapy.[1] We hypothesized that the presence of one or more of these variant alleles in patients with DAH caused by oral anticoagulants also increases the risk of developing pulmonary fibrosis (incidence rate app. 20/100,000).[2] This is important as anticoagulant therapy is considered to be an additional strategy to treat IPF patients.[3] In contrast, Thomassetti et al. did not find a beneficial effect of anticoagulants.[4] It is tempting to speculate that an association with *VKORC1* and/or *CYP2C9* variant alleles might even be a risk factor for the development or exacerbation of IPF. Furthermore, it was accentuated that in DAH cases early recognition of the presence of one of the studied polymorphisms is important, because of a potential lethal outcome and the fact that simple vitamin K supplementation can be life-saving.[5] Vitamin K supplementation is expected to diminish the inhibitory activity and the relative day-to-day variability of coumarins and can significantly improve anticoagulation control in unstable patients.[5,6] Moreover, vitamin K also acts as an anti-oxidant, reducing oxidative stress and inflammation caused by the iron, released during the DAH episode.[7]

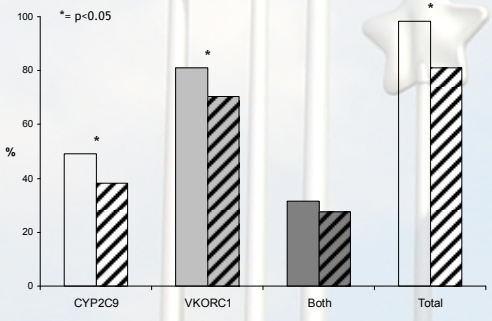
Aim

To study if patients using anticoagulants and experiencing at least one episode of DAH, associated with the presence of specific variant alleles, have a greater risk of developing subsequent pulmonary fibrosis.

Methods

During a 9-year period (7-year inclusion period and at least 2-year follow-up), data on patients using coumarins with confirmed DAH were gathered. Of 63 confirmed DAH cases receiving oral anticoagulants DNA was available. The reasons for the patients being on anticoagulants were: atrial flutter or fibrillation (n=28), myocardial infarction (n=13), chronic heart failure (n=6), pulmonary embolism (n=6), valve replacement surgery (n=5), deep-vein thrombosis (n=2), vascular disease (n=2), and hip-replacement (n=1). *CYP2C9**2/*3 (C430T/A1075C) and *VKORC1* (G-1639A/C1173T) SNPs were genotyped, using real-time PCR.

Figure 1: Polymorphism presence in DAH patients (n=63, solid) and in a normal population (n=173, striped).



Results

In 62 (98%) of 63 patients (age 62.9±15.8) with DAH, variant alleles were found (Figure 1). Out of these 63 DAH cases 34 (54%) subsequently developed pulmonary fibrosis. A total of 37 (59%) patients died within a 2±2 (range 0-10) year period after the DAH diagnosis was confirmed, and of the deceased, 18 (49%) developed pulmonary fibrosis. Additionally, 11 of the DAH patients received vitamin K supplementation, of whom three died to date (27%, see also Table 1).

Table 1: Patient characteristics of the DAH patients with and without pulmonary fibrosis.

	total DAH population (n=63)	fibrosis (n=34)	no fibrosis (n=29)
gender female/male	15/48	8/26	7/22
age diagnosis yr median/mean (range)	67/63 (20-85)	66/64 (22-85)	68/61 (20-80)
deceased no/yes	26/37	16/18	10/19
age death yr median/mean (range)	72/67 (20-92)	71/69 (29-92)	72/64 (20-81)
survival from diagnosis yr median/mean (sd)	4.0/4.5 (3.7)	4.5/5.1 (3.6)	2.0/3.8 (3.8)
year diagnosis median/mean (sd)	2003/2003 (3.0)	2003/2003 (2.8)	2004/2004 (3.3)
indication anticoagulant:			
coronary/vascular	54	30	24
pulmonary/thormbosis	8	3	5
other	1	1	0
vitamin K supplementation deceased no/yes	8/3	5/2	3/1
polymorphisms CYP2C9/VKORC1 number:			
none/one/both	1/42/20	1/19/14	0/23/6

Conclusions

- The incidence of pulmonary fibrosis in our studied DAH population was high compared with the incidence in a general population (54% versus 20/100,000, respectively).
- In case oral anticoagulants are considered in clinical practise, genotyping these *VKORC1* and *CYP2C9* SNPs is useful to predict the risk of bleeding complications, including DAH, and subsequent pulmonary fibrosis.
- Patients bearing both polymorphisms appeared to have a higher risk of developing pulmonary fibrosis.
- Vitamin K supplementation seems to be beneficial in patients bearing those SNPs, avoiding unstable or overshot target international normalized ratios (INRs) as well as oxidative stress, and should be considered.

References

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