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Identifying the Risk of Acute Exacerbation in Idiopathic Pulmonary Fibrosis

A Step Forward

The clinical course of idiopathic pulmonary fibrosis (IPF) is unpredictable (1), characterized in a significant number of patients by episodes of acute deterioration that heavily affects the prognosis of the disease. These events, named "acute exacerbations" (AEs), remain idiopathic in some cases, whereas in others, known risk factors, such as lung surgery, chemotherapy, radiotherapy, or other conditions, including pulmonary embolism, heart failure, and infections, are recognized (2). Nevertheless, the pathogenic mechanisms of AE in IPF remain largely unclear, causing a substantial lack of effective therapeutic approaches. In this issue of the *Journal*, McElroy and colleagues (pp. 550–562) explore in detail the role of the response to bacterial and viral infections in AE in patients with IPF (3). The starting point of this interesting research is a previous study published by the same authors showing that an SNP of Toll-like receptor 3 (TLR3), Leu412Phe (TLR3 L412F), is associated with a worse prognosis in patients with IPF (4). In the present study, this

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observation has been extended to establish if the same SNP could affect the response to infections and if that is associated with AE-related death in IPF (AE-IPF). To accomplish this, the authors studied 228 patients with IPF, and 107 of them were either 412F heterozygous or 412F homozygous. Interestingly, they report a significant increase of AE-related deaths in patients with 412F-variant IPF compared with patients with wild-type L412 IPF. The authors hypothesize that the increased risk of AE-related death in patients with 412F-variant IPF was related to some degree of inability to respond to infections. Indeed, they demonstrate that primary human lung fibroblasts, expressing the polymorphism, and derived from patients with IPF, have a reduced host immune response to different TLR pathogen-associated molecular patterns as well as a diminished transcription of IFN-stimulated genes, thus suggesting an impaired response to both bacterial and viral infections. The relevance of this observation is confirmed by a "hierarchical heat map analysis" performed by the authors on nasopharyngeal lavage samples of patients with IPF during AEs. The results of this analysis showed the contemporary presence of viruses and bacteria and, even more interestingly, specific combinations of them, such as influenza virus and *Staphylococcus aureus* or rhinovirus, respiratory syncytial virus, and *Streptococcus pneumoniae*. This intriguing observation was also supported by the analysis of bacterial populations in BAL of patients with IPF that revealed a specific bacterial profile, mainly composed of *Streptococcus* and *Staphylococcus* spp. in 412F-heterozygous patients as compared with L412 wild-type patients, where the level of *Prevotella* spp. was instead significantly higher. These data fully support the fascinating hypothesis that the TLR3 L412F polymorphism may alter the regulation of the lung microbiome, facilitating the occurrence of AE in patients with IPF.

On the basis of these results, McElroy and colleagues conclude that the TLR3 L412F polymorphism "is significantly associated with an enhanced risk of death by AE in IPF," stating that the main reason for this predisposition is related to a weaker antiinfective response due to the modified gene–environment interaction that characterizes patients with 412F IPF (3). The study can be considered a significant step forward in the understanding of some of those pathogenic mechanisms that contribute to explaining the occurrence of AEs in patients with IPF. The general topic of this article is within a very important area of investigation because the identification of the mechanisms behind AEs may help to improve the current therapeutic strategies. Some limitations of the study are also worthy of mention. Even if the total number of patients with IPF was high ($n = 228$), the number of AEs observed and studied was relatively low ($n = 8$). Moreover, although not considered as AE-related deaths, a total of 28 patients in the Edinburgh cohort died of pneumonia, and it should be underlined that in the case of pneumonia infections, the presence or not of the polymorphism and its supposed "predisposition" to infection was irrelevant. In the L412 wild-type group, 16 patients died of pneumonia, whereas 11 patients died of the same cause in the group of patients with 412F IPF. In addition, because of the lack of high-quality evidence, AE-IPF treatment can be very heterogeneous, potentially affecting both survival and microbiome balance. Because the use of antibiotics and/or steroids could have affected the microbiological results of the study, it would be important to have more information about the medical treatment of patients with IPF across the different cohorts of patients and, more specifically, if medical treatment was homogeneous in the K.U.M.S. cohort of patients with AE-IPF who had nasopharyngeal lavage samples, in the Brompton cohort of patients who had BAL samples, and obviously among the eight patients who died of AEs in the Edinburgh cohort. Furthermore, upper airway sampling, which according to the literature provides an imperfect but reliable representation of the BAL microbiota (5), was performed during the course of an AE-IPF. In contrast, in BAL, microbiological differences, both in bacterial burden and in bacterial populations, were detected in patients during a stable state. Indeed, it has previously been shown that in AE-IPF, the microbiome is substantially different, with an increased BAL bacterial burden and a shift in the composition of the respiratory microbiota compared with stable disease (6). There is another issue, already raised by the authors, that is worth further discussion. The authors investigated the role of the polymorphism exclusively on primary lung fibroblasts even if the *in vivo* pathogenic scenario could be much more complex. It is true, as underlined by authors, that fibroblasts are not merely bystander cells, but it is even more evident that airway epithelial cells and alveolar macrophages represent the very first line of defense against infections (7, 8). Both cells recognize and interact with pathogen-associated molecular patterns via a series of receptors, including TLR3, and thus actively participate in the inflammatory response to TLR agonists (9). In perspective, the role of their antiinfective activity should be investigated, possibly looking at the gene–environment interactions suggested in this study.

In conclusion, the results of this study are relevant because they identified for the first time an SNP of TLR3 that could represent a significant risk factor for mortality secondary to AEs in patients with IPF. However, these results need to be validated in larger studies, ideally using a prospective and multicenter design, with the aim to confirm the crucial role of this specific polymorphism in this deadly condition. ■

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How Many More Nights? Diagnosing and Classifying Obstructive Sleep Apnea Using Multinight Home Studies

Sleep duration, the proportion of REM and non-REM sleep, body position, and perceived sleep quality alter from night to night. It is not surprising that sleep disordered breathing varies too (1). Respiratory events may change across the night with the greatest changes in Sa_{O_2} seen during REM sleep (2). Obstructive apneas are more pronounced in the supine position, and other anatomical features such as nasal patency and upper airway collapse (3) can fluctuate night to night.

For clinical decision-making, any uncertainty in the apnea–hypopnea index (AHI) matters as the diagnosis obstructive sleep apnea (OSA) and its degree of severity are currently classified by simple cutoff values: mild OSA if AHI is 5–15, moderate OSA if AHI is >15–30, and severe OSA if AHI is >30.

Night-to-night variation in AHI is well established. Punjabi and colleagues (4) in a three-night study using a type III sleep apnea test showed 93% of those with a normal study on first night and 87% with severe OSA on first night were correctly identified compared with pooled values obtained over three nights. However, ~20% of patients with mild or moderate OSA on the first night were misdiagnosed or misclassified. A study (5) based on three nights of home testing using peripheral arterial tonometry showed that 24% of patients were misclassified using one night compared with three nights of data. Variability was partially explained by the duration of time spent supine. Notably, these studies, and those included in a meta-analysis and systematic review (1), observed night-to-night variation in AHI over a handful of nights with relatively small numbers of subjects.

In this issue of the *Journal*, Lechat and colleagues (pp. 563–569) set out to assess the prevalence of OSA (using a cutoff for diagnosis of AHI ⩾15), and night-to-night variation in AHI over a far longer period than in previous studies, and with a large sample size to understand the impact on diagnostic certainty (6). This was made feasible by using a contactless noninvasive diagnostic device (Withings Sleep Analyzer) placed under the user's mattress at home. Signals of body movement, respiratory rate, heart rate, snoring, and breathing pauses were used to calculate AHI, total sleep time, bedtime and waketime, and AHI using automated algorithms. Study data were obtained from 67,278 participants who used the device for more than 28 days; average use was very significantly longer than previous studies at 170 nights.

The authors examined the global prevalence of OSA in 20 countries in which at least 300 users had registered. They estimated overall prevalence of OSA in Japan to be 15%, the United States 21.6%, Germany 29%, France 23.1%, and the United Kingdom 22.9%. These findings are in line with the prevalence estimates of Benjafield and colleagues (7), although these present results should not be generalized, as the study group comprised self-selected individuals who purchased the under-mattress device so were likely to have had sleep-related symptoms and were therefore not a random sample.

Of key interest is whether extending the number of nights studied beyond a few nights minimizes potential misdiagnosis and misclassification. Clearly this seems most important when differentiating between no sleep apnea and mild OSA, and mild and moderate OSA. Here Lechat and colleagues add important clarity (6). They showed that an average of 21% of diagnoses (no OSA vs. OSA) would be false negative on a single night study. Severe OSA was correctly classified in 85% of cases, whereas mild and moderate OSA were correctly classified in only 54% and 52% of nights on a single night. Although data were obtained from the study group for 28 days to 8 months, the authors found that performance improved from 1 night of data to 14 nights of data, but beyond 14 nights there was no increase in area under the receiver operating characteristics curve and no further decrease in false negative and false positive rates.

What should the clinician take from this? First, that misdiagnosis and misclassification are relatively common after a

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