Personalized medicine in interstitial lung diseases

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Abstract

***Purpose of review**:* A number of recent studies have explored the possibility to apply personalized medicine to interstitial lung diseases (ILDs), particularly idiopathic pulmonary fibrosis (IPF), the most common and deadly of the idiopathic interstitial pneumonias. In our review, we summarize and discuss the most recent literature on personalized medicine in IPF as well as hypersensitivity pneumonitis (HP) and sarcoidosis, with emphasis on patient subgroups for which a personalized approach to disease prognostication and management may become a reality in the near future.

***Recent findings**:* Most of the studies that have explored the applicability of personalized medicine to ILDs have been conducted in patients with IPF. Such studies have suggested the existence of several distinct disease subgroups defined by similar genetic profiles, molecular pathways, exposures and individual lifestyles. Personalized medicine in HP is in its infancy. The development and applicability of personalized medicine to sarcoidosis, on the other hand, remains problematic for several reasons, including the lack of a diagnostic gold standard, the highly variable and unpredictable disease course, particularly across patients of different ethnicities, the poor correlation between disease activity and disease severity, and the lack of a validated management algorithm.

***Summary**:* A number of distinct patient subgroups have been identified in ILDs. While available data need to be validated longitudinally, the possibility to study homogeneous groups of patients may allow prediction of disease behaviour and response to treatment with dramatic clinical implications.

Keywords: interstitial lung disease, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, personalized medicine.

Introduction

Interstitial lung diseases (ILDs), also referred to as diffuse parenchymal lung diseases (DPLDs), are a large and heterogeneous group of disorders characterized by varying degrees of inflammation and fibrosis, often sharing similar clinical, physiologic and radiological features. A broadly used classification categorizes ILDs as idiopathic interstitial pneumonias (IIPs), of which idiopathic pulmonary fibrosis (IPF) is the most common and severe; diseases related to connective tissue diseases (CTD-ILDs), drug intake, and occupational and environmental exposures; and sarcoidosis (1). Despite a steadily growing interest and clinical research in ILDs, patient management remains suboptimal, mainly because of the limited knowledge of disease pathogenesis and the highly variable and unpredictable disease course (2).

Personalized medicine is a medical approach that emphasizes the customization of healthcare, with all decisions and practices being tailored to individual patients (3). The first step in personalized medicine is the identification of biological markers (e.g., biomarkers), which, broadly speaking, can be defined as measurable factors - most often proteins, found in blood, body fluid, or tissue but which can be also physiological measures such as forced vital capacity (FVC) or imaging measures - that carry information about the health or disease state of the individual assayed (4). Personalized healthcare has been successfully applied in a number of diseases, including cancers (5), although major scientific and logistical challenges still hinder its implementation in daily clinical practice (6). Whether a personalized approach to diagnosis and care can be applied practically and in a cost-efficient manner to ILDs is a matter of vivid debate (7).

In the past few years, the role of biomarkers in ILDs has been increasingly appreciated, and clinical applicability of some such markers in the near future can be anticipated. In this review, we summarize recent data on promising candidate biomarkers in ILDs and discuss their potential to revolutionize our approach to disease classification, diagnosis and treatment.

Idiopathic pulmonary fibrosis

IPF is the most common and deadly of the idiopathic interstitial pneumonias (8), with an estimated prevalence of 18-63 cases per 100,000 and 6-17 new cases per 100,000 yearly (9, 10). True epidemiologic data remain difficult to ascertain however, as common case finding methodologies were recently shown to have a marginal positive predictive value for IPF (11). Similar difficulties lie with disease prognostication. IPF has a highly heterogeneous natural history, whereby most individuals experience steady pulmonary function decline, some demonstrate relative stability and others die from rapidly progressive disease (12, 13).

Current clinical prediction models (14, 15) identify those at an increased risk of mortality, but fail to predict disease progression, as measured by pulmonary function decline (16, 17). These realities make IPF a frustrating disease for patients and clinicians alike, and have led to substantial investigation aimed at identifying subgroups that display differential outcomes and treatment response. Such investigation forms the backbone of personalized medicine in IPF, which aims to optimize disease prognostication and management by incorporating environmental, phenotypic and biomarker data into risk stratification models and treatment algorithms. Below are examples of promising subgroups for which personalized medicine may soon become a reality.

Gastroesophageal Reflux/Hiatal Hernia Subgroups

Gastroesophageal reflux (GER) is among the most commonly encountered co-morbid conditions in patients with IPF and represents a potential cause of IPF via alveolar injury from aspirated stomach contents (18). Though estimates vary, GER has been described in up to 87% of individuals with IPF using 24-hour esophageal PH monitoring (19). Asymptomatic GER and non-acid GER are also common in IPF (19, 20), complicating the manner in which GER is diagnosed and prevalence determined. In addition to GER, a large minority of patients with IPF also suffers from a hiatal hernia, which may exacerbate GER and further contribute to microaspiration (21, 22).

GER is typically treated with antacid therapy, including proton pump inhibitors and histamine-2 blockers. Data regarding the benefit of such therapy is conflicting and currently limited to retrospective analyses (23-25). While initial studies suggested improved outcomes in those treated with antacid therapy (23, 24), a recent post-hoc analysis of pooled IPF clinical trial datasets failed to replicate these findings and demonstrated an increased incidence of pulmonary infections (25). Formal testing of antacid therapy is underway in a phase II clinical trial titled "Pilot Trial of Omeprazole in Idiopathic Pulmonary Fibrosis (PPIPF)(NC02085018). While the results of this investigation will no doubt be informative, the concern remains that acid blockade fails to prevent the aspiration of stomach contents, irrespective of content acidity. As such, the mechanical correction of GER is also under investigation in a phase II clinical trial, titled "Treatment of IPF with Laparoscopic Anti-Reflux Surgery (WRAP-IPF)(NCT01982968). In addition to laying the foundation for larger, phase III trials, these investigations will begin to delineate whether such interventions benefit IPF subgroups with comorbid GER and hiatal hernia.

Airway Microbiome Subgroups

Microbes have long been implicated in the pathogenesis of IPF. Early studies suggested a potential role for several human herpes viruses, as these were found in higher proportions of individuals with

IPF than control subjects (26-31). Whether such viruses lead to the alveolar injury characteristic of IPF remains unclear however. Recent investigations of the lower airway microbiome have shed light on bacterial pathogens as well. Molyneaux and colleagues demonstrated a more than two-fold higher bacterial burden in the bronchoalveolar lavage fluid of patients with IPF compared to control subjects (32). Furthermore, increasing bacterial burden predicted both pulmonary function decline and death in this IPF cohort. In a similar investigation, Han and colleagues showed that the presence of *Streptococcal* and *Staphylococcal* species predicted IPF progression and reduced progression-free survival (33). These findings, in addition to a recent randomized placebo-controlled trial showing that co-trimoxazole may improve survival in IPF (34), support an upcoming, phase III multi-center clinical trial titled "Clinical Efficacy of Antimicrobial Therapy Strategy Using Pragmatic Design in Idiopathic Pulmonary Fibrosis" (CleanUp) (NCT02759120). This trial will not only determine whether antimicrobials represent an efficacious adjunct to anti-fibrotic therapy in IPF, but will also allow for the testing of such therapy in pre-specified, microbiome-derived subgroups.

Genetic Subgroups

While environmental risk factors have long been known in IPF, genetic risk factors have only recently begun to be delineated. Genome-wide association studies (GWAS) identified single nucleotide polymorphisms (SNPs) across multiple loci to be associated with IPF susceptibility (35, 36). Several SNPs are located on the short arm of chromosome 11, within *MUC5B* and *TOLLIP*, both of which play vital roles in airway host defence (32, 37-39). A recent investigation by Fingerlin and colleagues identified an additional novel locus within human leukocyte antigen (HLA) complex, underscoring the potential role that impaired host defense plays in IPF pathogenesis (40). In addition to their association with IPF susceptibility, SNPs within *MUC5B* and *TOLLIP* have also been linked to differential survival, though the strength of association varies depending on the cohort under consideration (36, 41-43). A recent pharmacogenetic investigation (44) also showed that a common SNP within *TOLLIP* may also modulate the response to *N*-acetylcysteine therapy, an antioxidant commonly used to treat IPF before a phase III clinical trial failed to demonstrate efficacy (45). While such outcomes analyses are novel, they are reliant on SNPs linked to IPF susceptibility. Given the aforementioned heterogeneity in IPF natural history, a genome-wide investigation aimed at identifying SNPs specifically linked to IPF outcomes would greatly enhance our ability to incorporate genetics into risk stratification models. Such work would also synergize with current gene expression work aimed at predicting mortality (46), and allow for the testing of IPF-specific therapies in cohorts genetically predisposed to a poor outcome.

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (HP) is an interstitial lung disease triggered by inhaled antigens, with multiple known causative agents. Recently Cramer *et al* studied the risk of HP among pigeon breeders in a retrospective study and identified an adjusted HR of 14.36 (95% CI 8.10-25.44) for HP and other ILDs for pigeon breeders (47). Whilst still rare, this finding suggests that protective measures should be considered among pigeon breeders to minimise antigen exposure.

Diagnosis of HP can be challenging, with wide variability in clinical, radiographic, and pathologic findings and a possible initiating antigen identified in only around 50% of cases (48, 49). To aid diagnosis of HP, Johannson *et al* have proposed clinical prediction models (cross-validated C-statistic 75.2 - 78.0) incorporating only clinical and radiographic features including age, history of down feather and/or bird exposure, and presence of ground-glass opacity and mosaic perfusion on chest CT (50). A group of patients with chronic HP develop progressive fibrosis with associated morbidity and mortality. Long *et al* have identified that baseline serum levels of YKL-40, a chitinase-like protein mainly secreted by macrophages, neutrophils, and epithelial cells, were significantly higher in patients with chronic HP than healthy controls, and patients who progressed or died had higher baseline YKL-40 levels than those who remained stable and survived (51). This finding requires external validation; however, it suggests that serum YKL-40 may have utility as a prognostic biomarker in HP patients.

The standard of care for chronic HP is antigen removal and corticosteroids; yet, the antigen may not be identified and patients may continue to progress or have corticosteroid related side effects. Alternative evidence-based therapeutic approaches are therefore required. Morisset *et al* performed a retrospective multi-centre study of the cell cycle inhibitors mycophenolate mofetil (MMF) and azathioprine (AZA) (52). Longitudinal trajectories in lung function were analysed prior to, and after treatment initiation. Both treatments were generally well-tolerated. No change in lung volumes (FVC) was identified; however, there was an improvement in gas transfer (diffusion capacity of the lung for carbon monoxide) of 4.2% ($p<0.001$) after 1 year of treatment. These retrospective data are supportive of the need for prospective randomised clinical trials to study long-term efficacy of MMF and AZA in chronic HP.

In patients with advanced, chronic HP lung transplantation may be considered, however data on outcomes following transplantation has been limited. Kern *et al* performed a single centre retrospective analysis of all patients undergoing transplantation with a diagnosis of HP (53). 31 subjects with HP had undergone transplant, with the diagnosis made only at explant in 5 cases. At 5 years, post-transplant survival was 67% (compared with 49% in a group of patients with IPF). In

two patients a recurrence of HP in allograft was identified, demonstrating the need for vigilance for ongoing antigen exposure and disease recurrence following transplantation for HP.

Sarcoidosis

Sarcoidosis is a systemic granulomatous disorder with a wide-ranging pattern of presentation and severity (54). While the cause of the disease remains unknown, a large body of evidence indicates that susceptibility to sarcoidosis is genetically determined (55). The disease however is not caused by defects in a single major gene or chemical pathway; instead, it results from a complex interaction between environmental/infectious agents and multiple genes, some with a major disease effect, but many with a relatively minor effect (56). Genetics is also believed to contribute to the highly variable clinical manifestations and prognosis of sarcoidosis (56).

Consistent with the concept that sarcoidosis granulomatous inflammation results from an abnormal immune response to persistent antigenic stimuli, several HLA alleles have been associated with the disease (55). However, there is considerable variability in the alleles that are associated with increased disease risk or "protection" across different ethnicities, which makes personalization of genetic susceptibility/protection very challenging at this moment. There is one situation, however, in which a genetic association is robust across different populations, and is practical and clinically relevant. This is the HLA-DRB1*0301 (DR3) association with Löfgren's syndrome, an acute and almost invariably benign form of sarcoidosis that manifests with fever, bilateral hilar lymphadenopathy and erythema nodosum with or without periarticular inflammation of the ankles (57). Notably, approximately 50% of individuals who present with Löfgren's syndrome but do not carry the DR3 allele experience persistent disease and a less favourable outcome (57).

Recent studies have highlighted the potential of immune mediators and immunogenetics in determining disease development and behavior, and guiding treatment in sarcoidosis. Levin and colleagues genotyped a large population of African American patients (n=1,277) and matched controls (n=1,467) (58), and found that, consistent with previous findings among individuals of European descent (57), carriage of the HLA-DRB1*0301 allele is associated with a resolving disease course. Owing to the high likelihood of experiencing a self-limiting disease course, treatment may be contraindicated in sarcoidosis patients carrying the HLA-DRB1*0301 allele.

Fischer and co-workers recently performed the largest sarcoidosis case control study to date. In the screening step, they genotyped a European cohort of 1,726 patients and 5,482 controls using the Illumina Immunochip SNP array (59), while multiple European cohorts and one African American cohort were used for replication and subgroup analysis. They identified novel disease susceptibility loci with genome-wide significance at 12q24.12 (ATXN2/SH2B3), 5q33.3 (near IL12B), 4q24

(MANBA/NFKB1), 2q33.2 (FAM117B), and 1p31.3 (IL23R) along with three independent signals in the HLA region. Notably, this study suggests a significant genetic overlap between sarcoidosis and other immune-mediated inflammatory disorders, thus providing hypotheses for novel therapeutic targets.

As with other ILDs, the main goal of personalized medicine in the management of sarcoidosis is the identification of biomarkers to predict disease behaviour and response to treatment. Indeed, it is well known that a person's genes influence their responses to drugs, both in terms of therapeutic effect and adverse effects. Testing leukaemia patients for their thiopurine S-methyltransferase (*TPMT*) status is one of the most common examples of treatment being tailored to match patients' genetics (60). In sarcoidosis, *TPMT* genotype may potentially affect response to thiopurines such as azathioprine and methotrexate, two commonly used second-line steroid-sparing agents (61, 62), although this has never been formally addressed in adequately powered clinical studies. Patients who experience disease progression despite (or intolerable side effects from) conventional therapy are usually treated with anti-tumour necrosis factor (TNF) monoclonal antibodies, especially in organ-threatening or life-threatening disease (63). Wijnen and colleagues evaluated the contribution of TNF-a G-308A genotype to response to anti-TNF-a treatment in 111 patients with refractory sarcoidosis (64). They observed that individuals homozygous for the G allele were more likely to respond to anti-TNF treatment (either infliximab or adalimumab) compared to carriers of the AA or GA genotype. Personalized prescribing has the potential to revolutionize the landscape of sarcoidosis treatment; at present however there is very limited evidence for it to be applied to clinical practice (65).

The development and applicability of biomarker tools to sarcoidosis remains problematic for several reasons, including the lack of a diagnostic gold standard; the highly variable mode of presentation, manifestations and outcome; the poor correlation between disease activity and disease severity; and the lack of a validated management algorithm (66). As such, the added value of biomarkers over the standard clinical assessment in patients with sarcoidosis remains to be established.

Conclusion

Over the past few years, genetic and molecular approaches have improved dramatically our knowledge of the genetic heterogeneity of ILDs, particularly IPF. These studies have suggested the possibility to stratify patients on a pathway-specific basis, thus allowing for the testing of therapies in more homogeneous cohorts. Disease prognostication and management will also benefit from incorporation of environmental and phenotypic data into risk stratification models and treatment

algorithms. The importance of personalized medicine in ILDs remains to be established and much work is needed to prospectively validate available data. If successful, however, this approach has the potential to transform the diagnosis, classification and management of these challenging diseases.

Key points

A number of biological molecules with potential utility for the diagnosis, assessment of disease activity, prediction of disease behaviour, and response to treatment have recently been evaluated in interstitial lung diseases (ILDs).

The possibility to apply personalized medicine to ILDs has been explored more convincingly to idiopathic pulmonary fibrosis (IPF), wherein distinct disease subsets – defined by different genetics, molecular pathways, exposures and patient lifestyles – have been described.

A growing body of evidence suggests that patient genetic make-up may be important in treatment decision-making by defining subgroups of patients that share specific pathogenetic profiles and are therefore more likely to respond to a given therapy.

At present, no biomarker is ready for routine use in clinical practice or trials of pharmacological interventions, but a number of biomarkers that are currently being validated in longitudinal studies may be available in the near future.

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Dr. Spagnolo has served as consultant for InterMune, Roche/Genentech, and Santhera Pharmaceuticals, has served on scientific advisory boards for Boehringer-Ingelheim, and has received speaking honoraria from InterMune, Roche/Genentech, Boehringer Ingelheim, Zambon and Novartis.
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