
Is sarcoidosis ready for personalised medicine?

By definition, sarcoidosis is a multisystem disorder. Practically no organ is immune to sarcoidosis. Appropriate multidisciplinary management is mandatory and attention must be paid not only to the somatic aspects of the disease but also to the psychosocial components of this often elusive disorder. The indications for treatment for the individual patient depend on many factors, not just whether or not the patient is symptomatic but also whether or not there is evidence of asymptomatic significant disease, especially in vital organs; careful considerations needs also to be given to the likely benefits of any therapy set against the risk of adverse events. The scene is therefore set: is sarcoidosis ready for personalised medicine?

BY PROF. DR. ROLAND M. DU BOIS

Sarcoidosis is a systemic granulomatous disease that is characterised by a highly variable pattern of disease presentation, involving more than one organ of the body, and by a wide range of disease severity. Although the lung is most commonly affected this is not invariable and when it is affected the amount of disease can range from minimal involvement to life-threatening fibrosis with the risk of pulmonary hypertension (see figures 1 and 2). It stabilises or improves in many cases, but may worsen and become chronic in others. Devastating extra pulmonary complications may become apparent.

There have been many reports of the association of genetic variants with particular patterns of organ involvement; these associations vary from country to country probably due to the inherent differences in gene pools across ethnic boundaries but some associations are common to different ethnic groups. The cause of the disease is unknown but because of the similarities of the granulomatous histopathology of sarcoidosis with diseases that are known to be caused by certain microbial infections, including tuberculosis, it is suspected that sarcoidosis may be triggered in many instances by exposure to one or more micro-organisms but more definitive evidence is still required (see figure 3).

This disease is, therefore, highly complex in terms of



Ron du Bois is Emeritus Professor of Respiratory Medicine, Imperial College, London. He was previously Professor of Medicine in the Department of Medicine at National Jewish Health, Denver, Colorado and Consultant Physician at the Royal Brompton Hospital, London UK. He qualified from Cambridge University and trained in general and respiratory medicine in London. After a two-year period as visiting scientist in the Pulmonary Branch of the National Heart, Lung and Blood Institute at the National Institutes of Health, Bethesda, Maryland, USA, he returned to London to develop his clinical and research interests in the genetics, pathogenesis and treatment of Interstitial Lung Diseases at the Royal Brompton Hospital where he was head of the Interstitial Lung Disease Unit and the Clinical Genomics Group. He is author of over 250 peer-reviewed articles. He has served as a member of The BTS Orphan Lung Diseases Committee, the ATS Planning and Nominating Committees, the ERS Council and was a Medical Advisor to the Raynaud's and Scleroderma Association, UK, for more than a decade. Dr. du Bois is advisory board chair or member for several studies of novel therapy for interstitial lung diseases, including idiopathic pulmonary fibrosis. e-mail: ron@du-bois.co.uk

predisposition, triggers, mode of presentation and severity and thus there is no approach to diagnosis and management that fits all cases; there is need for a more individualised process that addresses each individual's requirements with no redundancy of investigation and, probably more importantly, no unnecessary treatment with its risk of adverse events – personalised medicine.

The founder of WASOG – the World Association of Sarcoidosis and Other Granulomatous Diseases, an association that now embraces all interstitial lung diseases – the

late Professor D. Geraint James was a wonderful protagonist of the concept of individualised medicine. A phrase often cited by him, “all that glitters is not sarcoidosis” embodied the need for precision of diagnosis and inherent in this is the need for precision of pattern of disease identification and precision in the treatment approach that must put the patient at no extra risk by being on therapy than they would experience without treatment.¹

In memory of Gerry James, the Second joint meeting of the 10th WASOG Meeting and 12th BAL Meeting, held in Maastricht, the Netherlands, between June 15-18th,

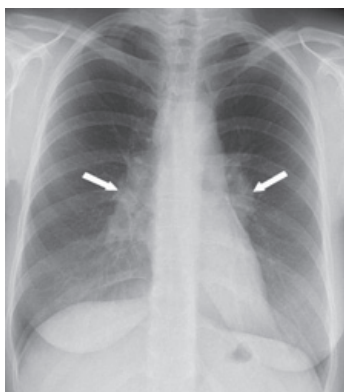


Figure 1. Chest radiograph of a patient with Löfgren's syndrome, showing bilateral hilar and right paratracheal lymphadenopathy, a pattern of disease that usually results in a good outcome.



Figure 2. Chest radiograph of a patient with extensive lung scarring. Note the fibrotic changes with loss of lung volume in the upper zones of both lungs. This is fixed and irreversible.

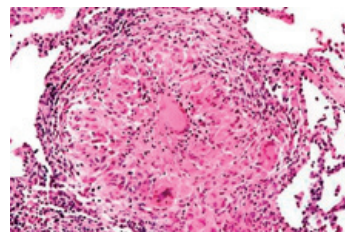


Figure 3. Lung biopsy sample from a patient with sarcoidosis showing the classical non-caseating granuloma, containing a giant cell, which is the histopathological hallmark of this disease.

2011, included a lecture named in his honour, the Honoured Gerry James lecture, delivered by the author of this review and on which this review is based. Gerry would have enjoyed the question posed by this lecture; are we ready for personalised medicine in sarcoidosis? To address the question it is necessary to put into perspective what personalised medicine is, how it has been applied, whether it can be used in the context of lung disease, including sarcoidosis lung disease, and, importantly, to sarcoidosis in general.

What is personalised medicine?

Personalized medicine is a medical model emphasizing in general the *customization of healthcare*, with all decisions and practices being tailored to individual patients in whatever ways possible. In a detailed perspective on the subject written jointly by the commissioner of the Food and Drug Administration, Silver Spring, Maryland, USA, Dr. Margaret Hamburg and the director of the National Institutes of Health, Bethesda, Maryland, USA, Dr. Francis Collins, the authors set out the need for a pathway to be built from the massive information data sets derived from genetic studies to a better clinical outcome for patients. They recognised the many obstacles that need to be surmounted before the full benefits of the research can be translated into clinical care.² Together, “...we have been focussing on the best ways to develop new therapies and optimise prescribing by steering patients to the right drug at the right dose at the right time”. Translating genetic association to molecular outcomes and thence to therapies designed to intervene in health care is just one of the facets of a more personalised medicine approach. Other factors that need to be considered are causation of disease, epidemiological factors including exposure or lifestyle risks, better screening and diagnostic tools in addition to more specific, targeted treatments.

Can personalised medicine be practical?

In the context of these major challenges, is there any hope that personalised medicine can be applied practically and in a cost-efficient fashion? There are numerous examples of initiatives that show convincingly the successful application of personalised health care and three of these will be described.

Prevention

The best way to tackle disease is to prevent it; attacking those factors that increase the risk of developing fatal diseases or the complications of disorders in, for example the vascular compartment is arguably the most sensible approach – prevention by early intervention on factors that increase risk of disease. This is encompassed by the NDDO Institute for Prevention and Early Diagnostics in the Netherlands and their “Preventie Kompas”. The goals of the institute were set out clearly at the Maastricht 10th WASOG Meeting and 12th BAL Meeting congress by Dr. Roderick A. Kraaijenhagen and, in brief, the mission is to provide an access to gaining personalised life style advice based on personal risk factors with a view to maintaining health rather than only treat the consequences of ill-health. The organisation has a web-based system to facilitate access. Obvious and key issues include cigarette smoking, obesity, hypertension, a sedentary life style; if factors such as these can be identified early and, with appropriate counsel, modified, the benefits are vast.

Breast and Ovarian cancer

BRCA1 (breast cancer susceptibility gene 1) and BRCA2 (breast cancer susceptibility gene 2) are human genes that belong to a class of genes known as tumour suppressors.

In normal cells, *BRCA1* and *BRCA2* help ensure the stability of the cell’s genetic DNA and help prevent uncontrolled cell growth. Mutation of these genes has been

linked to the development of hereditary breast and ovarian cancer. Women who possess the highest risk variants have an increased lifetime risk of breast or ovarian cancer. In this context the identification of these high risk variants on screening of an individual with a family history of breast or ovarian cancer affords the opportunity of personalising the steps that that individual may take in dealing with the risk, including more detailed monitoring or prophylactic surgery to remove the breasts or ovaries – not a trivial decision but aided by knowing from genetic testing that there may be an increased risk.

Other examples from the field of cancer include the use of the results of immunohistochemistry +/- genetic screening to indicate a more specific treatment: the use of trastuzumab (Herceptin) in metastatic breast cancer if the tumour shows evidence of human epidermal growth factor receptor type 2 (HER2) expression on immunohistochemistry or gene amplification; cetuximab (Erbix) if epidermal growth factor receptor (EGFR) is expressed on tumour immunohistochemistry in metastatic colorectal cancer; and imatinib (Gleevec) if the cell-surface tyrosine kinase receptor c-kit is expressed in gastrointestinal stromal tumours.² Taken together these are perfect examples of identifying a specific disease phenotype and developing therapies that attack targets specific to that phenotype.

The lung: idiopathic pulmonary fibrosis

Of the diffuse lung diseases (also known as interstitial lung diseases, ILD) idiopathic pulmonary fibrosis is the most frequent of the idiopathic interstitial pneumonias (IIP) that are characterised by widespread fibrosis, and is by far the most lethal with a 50% mortality at 2-3 years after diagnosis. For this reason it is imperative that this disease is differentiated from all of the other ILD with which it might be confused because this has obvious implications for discussions with the individual and his/her family about the likely outcome and a precise diagnosis

also has implications with regard to treatment recommendations now that there is an approved therapy in Europe for this disease – pirfenidone.³

Until recently, however, it has not been possible to provide a risk assessment that can be applied to an individual. It has long been known that in general idiopathic pulmonary fibrosis (IPF) carries a worse outcome than the other diffuse fibrotic lung diseases but for any given individual, what is the range of magnitude of risk?

In a recent publication, we have reported a mortality risk scoring algorithm using longitudinal data sets from two large but negative clinical trials of a potential novel therapy for IPF.⁴ A number of demographic and physiological variables were modelled and a simple risk assessment system derived from the four most informative of these indices was constructed. The four, easily measured, indices were: age; whether or not the individual had been hospitalised in the previous 6 months; the % predicted forced vital capacity, a measure of lung size that is reduced by the scarring process that is IPF; and the change in % predicted forced vital capacity in the previous 6 months. Each of these indices is scored, the scores are summed and this provides a range of risk of mortality in the subsequent 12 month period that is specific for that individual. This scoring system does need to be validated but, if it is confirmed, this could be a valuable tool in personalising predictions of disease outcome that will have obvious implications for counselling, decisions on treatment initiation or discontinuation and the timing of referral for transplant evaluation.

The challenge that is sarcoidosis Clinical Phenotype

The evidence is now clear that personalisation of medical care is not just advisable but is an imperative that we must achieve across the board. There exist, as discussed above, numerous applications of personalised medicine that already work. How does sarcoidosis measure up?

In the context of there being no definitive causative factors, a preventative approach is not possible, nor is genetic screening sufficiently specific except in one subset of disease that will be discussed later. Achieving global personalisation tools will therefore be a challenge especially when also considering the differences in genetic associations with sarcoidosis found in studies of individuals from different ethnic backgrounds, the known variations in predominant patterns of organ involvement at presentation in different countries and the varying rates of individual organ disease progression. Despite these challenges, there are some, relatively modest approaches to personalisation that can be applied and that will enhance patient care. For example, it has long been known that disease in certain organs, including the

central nervous system, certain patterns of eye disease and cardiac involvement carry a more guarded prognosis and thus require a different management and monitoring approach than more benign disease (see figures 4 and 5). A form of sarcoidosis, Löfgren's syndrome, which presents acutely with lumpy skin lesions known as erythema nodosum and/or bilateral ankle arthritis, fever and bilateral lymphadenopathy in the chest, is associated with a good outcome, especially if the individual carries a specific HLA-genotype (see later). The existence of lung fibrosis at presentation, especially when extensive, is associated with more protracted disease and a less benign outcome compared with a pattern of disease that includes little fibrosis (see figures 6 and 7).

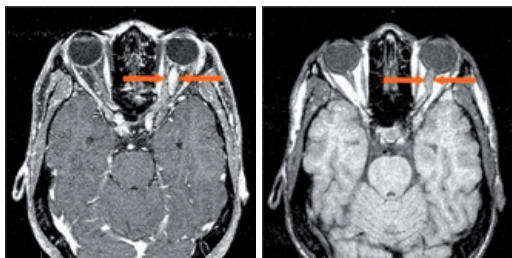


Figure 4. MRI scan of the brain of a patient with sarcoidosis of the optic nerve. Note the dense white regions of the brain (arrows) that represent the abnormal tissue.

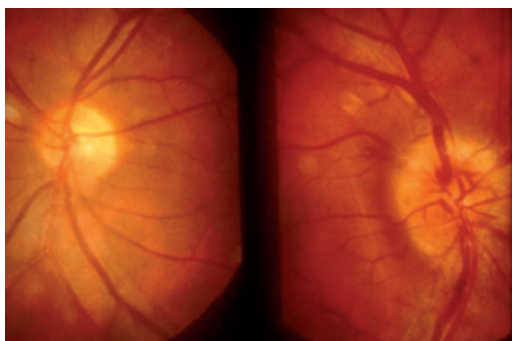


Figure 5. Optic nerve granuloma (right). Optic nerve on the left is normal.

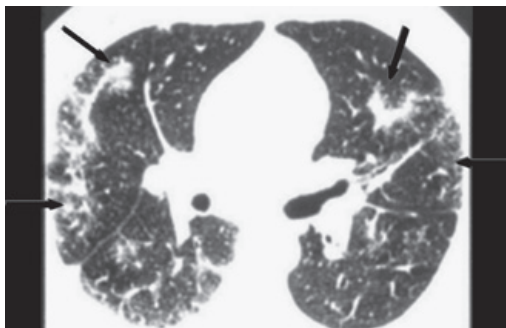


Figure 6. High resolution computed tomography (HRCT) scan of the lungs of a patient with sarcoidosis. The abnormal regions are indicated by arrows.

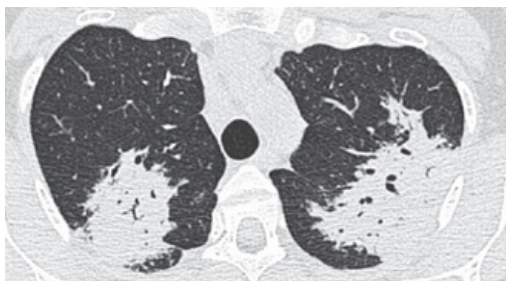


Figure 7. HRCT scan of the lungs of a patient with extensive fibrosis in both lungs, shown here as dense white infiltrates.

Another clinical phenotyping approach that has promise is one that includes a measure of disease progression and responsiveness to therapy in the process of individualising disease status. A recent international collaborative study has proposed a clinical outcome status classification comprising nine different patterns of sarcoidosis, independent of pattern of organ involvement, based on: the extent of disease in the involved organ(s); whether or not disease has resolved with or without therapy over a five year period; and whether or not continuing treatment is required.⁵ Application of this classification may be of value in the design of clinical trials and for stratifying patients' likely future treatment needs but still falls short of providing the degree of individualisation that would be ideal. In future, positron emission tomography may provide a more sophisticated measure of disease extent, distribution and reversibility that will inform a more personalised strategy but this field is at an early phase of application (see figure 8).

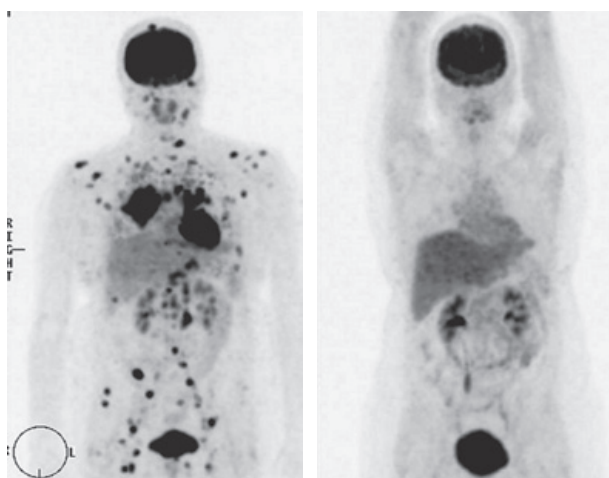


Figure 8. PET scan of a patient with widespread sarcoidosis, shown as the black lesions before (on the left) and after (on the right) corticosteroid therapy that resulted in marked resolution. Picture courtesy Fred Verzijlbergen & Jan Grutters, Nieuwegein, Netherlands.

A second classification system that is lung-specific has been proposed (Hamzeh, N; personal communication). This employs a system based on the severity of abnormalities of lung function indices together with the Scadding grade of abnormality on chest radiography to determine a composite score for assessment of global lung burden. The advantage of this system is that it inherently acknowledges that extensive radiographic disease is not always matched by severity of lung function impairment and vice versa, so that by using a combination approach a more accurate and global measure of severity can be achieved. This simple scoring system has been shown to correlate well with more complex exercise physiological measures of lung disease severity and thus holds promise for providing a simple individual severity score, especially if it can be validated in more than one centre.

Personalisation by Genetic Association

Consistent with the concept of sarcoidosis being the product of a persistent antigenic stimulus resulting in a granulomatous immune response, it is not surprising that the most significant and validated gene associations with sarcoidosis are with alleles of the major histocompatibility locus (MHC) genes on chromosome 6, encoding proteins that present antigen to T cells.⁶ However, there is considerable variability in the genes that are associated with susceptibility or “protection” across different ethnic populations, which makes personalisation of susceptibility very inexact at this time. However, there is one situation where a genetic association is robust across different populations, predicts the likely outcome in a subset of sarcoidosis and has been applied in clinical practise. This is the MHC association with Löfgren's syndrome. A number of studies particularly from Sweden, the Netherlands and the UK have shown that a combination of the class II MHC alleles, HLA-DQB1*0201 and HLA-DRB1*03 appears to increase

the risk of developing Löfgren's syndrome, an acute presentation of sarcoidosis that generally carries a good prognosis.⁷ However, in individuals with Löfgren's syndrome but without this genetic type, the outcome is less good and disease can be more persistent. Because of this prediction of outcome and its clinical implications, genotyping for this allelic combination has now been incorporated into a more personalised staging process for patients with Löfgren's syndrome in clinical practise at the Karolinska Institutet in Stockholm – the first clinical application of genetics in sarcoidosis.

The TNF-alpha-gene and treatment strategies

It is not only the MHC genes that are located on chromosome 6 but also the genes that encode the TNF-proteins. Alleles of the TNF-alpha-gene are often found to be in linkage disequilibrium with HLA alleles, being inherited together more frequently than would have been expected from a random association. One frequently studied region of the TNF-alpha-gene is the promoter region where differential protein binding, dependent on gene sequence, has an effect on the rate of gene transcription. It has been shown that allelic variants in this region are associated with a variety of chronic inflammatory lung diseases including sarcoidosis. As TNF is a key protein in the early inflammatory response in sarcoidosis, it follows that genetic variants that affect its production or agents that block its action may be important for sarcoidosis. One study of non-sarcoid individuals showed that whole blood cells from those who had the A allele at position -308 in the TNF-promoter region synthesised greater amounts of TNF after stimulation than cells from individuals who did not have this allele.⁸ In a study of the impact of infliximab, a TNF-antagonist, in sarcoidosis it has been shown that the administration of the antagonist improved the rate of lung function change in sarcoidosis patients compared with those on placebo.⁹ In a separate

study of serum samples taken from individuals recruited to this efficacy and safety study, lower forced vital capacity measures were found at baseline in those with higher TNF baseline serum concentrations and there was a greater infliximab effect on lung function in those individuals with the higher serum concentrations.¹⁰ A direct genetic association of the -308A, and indeed any other, TNF-allele with treatment response has not, however, been demonstrated in these patients. The evidence is thus circumstantial for a genetic relationship between TNF-alleles and TNF-antagonism in sarcoidosis. Can any supportive evidence be obtained from other chronic inflammatory diseases? The data are generally negative. In rheumatoid arthritis, for example, there is no evidence that an A allele at position -308 is associated with a better response to any TNF-alpha-inhibitor.^{11,12} In this context, therefore, although there are no genomic indicators for any specific therapy in sarcoidosis thus far, including TNF-antagonism, this will undoubtedly form part of a future where gene and protein markers will be used to define disease types, predict progression and the need for therapy; the future will also undoubtedly include pharmacogenetic profiling that predicts the likelihood of an individual responding to a proposed therapy and their risk of an adverse response to that therapy.



Final reflections

Sarcoidosis is a multi-organ disorder and the first manifestation of the disease can occur in any organ. Individuals with sarcoidosis may, therefore present for the first time to any one of a variety of organ specialists and the management of their disease often requires a multidisciplinary approach. The cornerstone of disease management involves careful baseline assessment of disease distribution and severity by organ, with emphasis on vital target organs. Because the clinical course can be unpredictable, regular monitoring for signs of disease progression in known organs of involvement and the development of disease in different organs is necessary. Is sarcoidosis ready for personalised medicine? The answer is, of course, yes but we do not have anywhere near enough tools at present to implement a personalised strategy except in very limited circumstances. We need globally tested classification systems to provide robust phenotypes that include patterns of organ involvement and longitudinal behaviour and we need much more specific links between molecular and clinical science. So, in summary, certainly ready, but not yet able.

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