Topical Review

Personalised Medicine for Multiple Sclerosis Care

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Abstract

Background

Treatments with a range of efficacy and risk of adverse events have become available for the management of multiple sclerosis (MS). However, now the heterogeneity of clinical expression and responses to treatment pose major challenges to improving patient care. Selecting and managing the drug best balancing benefit and risk demands a new focus on the individual patient. Personalised medicine for MS is based on improving the precision of diagnosis for each patient in order to capture prognosis and provide an evidence-based framework for predicting treatment response and personalising patient monitoring. It involves development of predictive models involving the integration of clinical and biological data with an understanding of the impact of disease on the lives of individual patients.

Objective

Here we provide a brief, selective review of challenges to personalisation of the management of MS and suggest an agenda for stakeholder engagement and research to address them.

Personalised medicine for MS: is it needed?

Personalised medicine is currently in vogue. It has been championed as a foundation for future medicine, based particularly on examples drawn from cancer and rare inherited metabolic diseases[1]. Individualized, genetic based diagnoses have had considerable impact, e.g., in licensing of imatinib for Philadelphia chromosome positive chronic myeloid leukaemia and trastuzumab in HER2 positive breast cancer[2]. Whole exome or whole genome sequencing promises further impact on diagnosis and management of rare diseases[3].

But, is it needed for those of us caring for people with multiple sclerosis (MS)? There is no question but that MS care is an area that should be the focus of innovation in the model for healthcare delivery. MS is a 'syndrome' with a wide variation in clinical presentation, disease course and responses to treatments. While unpicking this heterogeneity may not have been crucial twenty years ago, when limited treatment options were available, with an increasing number of available treatments and a more empowered and informed patient population, it is central everyday practice now. Because the medicines all are relatively expensive, better ways of making most effective use of them are needed (Fig. 1A). They also have different mechanisms of action and a wide range of efficacy and relative risk. A newly diagnosed patient and his or her neurologist therefore must make complex decisions for treatment initiation, treatment choice and treatment escalation. The neurologist needs to define and communicate clearly to patients and payers:

- *What* factors contribute to the expression of MS and its relative risk without treatment?
- *Who* should be treated?
- *When* should they be treated?
- *How* can medicine risk and benefit best be balanced?

The patient and the payer both need to be confident that neurologists' answers to these questions are well founded. These questions can be answered with reference to clinically meaningful characteristics of sub-groups of patients. However, this alone does not ensure that the needs of all individuals are optimallly addressed. The goals of personalised medicine are to establish robust, evidence based approaches to addressing the questions for each patient.

Recent advances in the management of other complex diseases offer real cause for optimism that these goals are achievable. Rheumatoid arthritis (RA) provides an illustrative example. Individual differences easily captured in the clinic define different disease courses and can be used prospectively in the selection of treatments. Epidemiological studies showed that patients with high body mass index have worse outcomes from RA and may respond more poorly to tumour necrosis factor inhibitors (TNFi), whereas the efficacy of abatacept and tocilizumab is unaffected[4]. Smoking also adversely affects TNFi outcomes, but has less or no effect on the efficacy of rituximab and tocilizumab. Patients expressing an anti-citrullinated peptide antibody biomarker are more likely to have a progressive, destructive course[5] with greater disease activity and radiological damage[6] and a worse response to anti-TNF medications[7], although a better response to rituximab and abatacept[8].

Where are we now?

The questions posed for personalized medicine for MS now can be distilled into three challenges:

- Precision diagnosis
- Predicting treatment response
- Personalised monitoring to progressively update this prediction

Briefly reviewing progress towards realising these provides a way of benchmarking the current state of the art.

Diagnosis couples clinical presentation with conventional laboratory tests and imaging (and, in some cases, cerebrospinal fluid (CSF) examinations)[9], to reject alternative possible disorders, define the probable MS syndrome and, in some cases, to recognize the distinct sub-syndrome of primary progressive MS. Auto-antibody testing supports further diagnostic precision that defines distinct diseases amongst the idiopathic demyelinating disorders. Neuromyelitis optica spectrum disorders (NMOSD) can now be identified by serum antibodies against aquaporin4 (AQP4-IgG) with high specificity[10, 11] and moderate sensitivity[12]. NMOSD have a distinct clinical course to MS and do not respond (or may worsen) with IFN treatment[13]. Patients with MOG antibody-associated demyelination also have a unique clinical, radiological, and therapeutic profile[14]. These examples illustrate well how the integration of clinical and biomarker data can be used to provide specific prognostic and therapeutic advice to individual patients.

However, where we still fall far short of the ideal is in establishing prognosis, which also should be part of *precision diagnosis*. Because all treatments carry costs – in financial terms or as a reduction in quality of life or risks to future health- the *net* benefit of treatment involves balancing the expected natural history of an individual's disease, or baseline risk, against the effects of treatment[15] (Fig. 1B). Patients differ widely in their baseline risk of untreated disease progression. The net benefit of any treatment needs results from the interaction of treatment efficacy and likelihood of adverse events against baseline risk. It is this net benefit that is central to estimates of clinical effectiveness.

Considerable community effort has been addressed to the identification of prognostic factors for estimation of the baseline risk, but the precision with which this can be done still is limited. For example, MRI measures of disease activity (by gadolinium contrast enhancement) or T2-hyperintense lesion load are important prognostic measures for prediction of risk of clinically definite disease after first symptoms[16]. Large, single clinical centre-based studies additionally have highlighted interactions of MRI measures with age and sex in determining risk of progression[17]. Lesion distribution or clinical presentation appear to be independent predictors of medium term prognosis[18]. Epidemiological studies suggest that other phenotypic (e.g., obesity, serum vitamin D), exposure (e.g., sunlight) and lifestyle factors (e.g., smoking) impact on prognosis[19]. However, we are not aware of models that define their quantitative interactions with individual susceptibilities. For example, is the impact of smoking, low vitamin D and obesity meaningfully higher in people carrying the DRB1501 allele, or with early presentations of disease? Genotype alone has not yet been shown to contribute significantly to disease severity risk[20]. In the absence of single, highly predictive markers, personalisation will depend on clusters of markers in multivariate models.

There still are few specific indices to guide the timing of treatment beyond evidence from trials that early treatment delays short-term clinical progression[21]. Choice of initial treatment also does not have a good evidence base, other than the lack of benefit (or worsening) that has been found with IFN and other conventional disease modifying treatments[22] in patients with progressive onset disease or NMOSD. While not fully evidence-based, patients with a higher baseline risk likely will receive greater *net* benefit from any treatment. Information concerning the relative efficacy of medicines is limited due to the small number of head-to-head clinical trials and the limitations of inference even when comparisons of the

pivotal trials of individual agent efficacies are made using formalized meta-analytic structures[23]. One of the most promising approaches to gathering evidence concerning relative clinical effectiveness is through real-life data aggregation in multi-centre consortia, such as MSBase [24]. Generally, choices regarding medicine use in clinical practice are framed in terms of a hierarchy of efficacy and risk for treatments based on data from their pivotal clinical trials (which were intended to demonstrate efficacy, rather than comparative effectiveness). Decision-making then represents the balancing of these data against estimates of relative disease severity for any given patient. Patient and neurologist specific factors of preference and access also play a role. However, while there may be general guidelines, there is not a general consensus regarding the criteria and methods for arriving at the balance of evidence for an individual patient.

Although pharmacogenomics has been of limited use thus far in the personalisation of MS, this could change, particularly if the medical community moves towards more routine genotypic profiling. Individual characteristics determining drug metabolism (e.g., hepatic and renal function for elimination of IFN) may guide choice of drug in less common situations in patients with comorbidities[25]. Differences in ethnicity may alter drug absorption or metabolism[26]. There is preliminary evidence for possibly meaningfully significant effects of specific markers in some individuals for IFNβ[27-29]. For example, one study reported the discovery and validation an intronic variant in SLC9A9 gene as response predictor ($P < 5 \times 10^{-8}$)[30].

Currently, in the absence of strongly predictive prospective markers, treatment *monitoring* plays a major role. In fact, unquestionably the currently best developed example of personalized medicine in MS is for safety monitoring of natalizumab treatment[31]. This model combines titres of anti-JC virus antibody, treatment duration and previous history of immunosuppressive therapy in order to stratify patient risk of progressive multifocal leukoencephalopathy (PML). Baseline risk assessment and monitoring with treatment rapidly became the standard of practice as the manufacturer and regulators worked together to define a way of keeping this powerful treatment available once PML was recognized as a complication. An international pharmacovigilance effort developed by the manufacturer rapidly led to validation of a clinically practical approach to personalization of risk and subsequent monitoring.

Monitoring for effectiveness is more challenging, in no small part because the target outcome (ultimately, the accrual of fixed disability) is less easily defined. Nonetheless, there are examples that are widely, if not

universally, employed. Neutralising antibody levels for IFN[32] and for natalizumab[33] explain a major proportion of poorer efficacy of these medications. More generally, T2 lesion increases and brain volume reduction on treatment are predictive of longer term clinical efficacy, at least at a group level[34]. The latter, combined with clinical measures of disease activity (relapse frequency or progression of fixed disability) already are incorporated into treatment escalation decisions in many clinical centres, although specific criteria for a switch in treatment are not generally agreed. While the availability of large datasets is a major confound, this also is a consequence of lack of standardization of MRI field strength, criteria for lesion identification and software for brain volume change measures. Possibly even more sensitive markers of sub-clinical disease activity are emerging, e.g., with monitoring of CSF or serum neurofilament light chain (Nf-L) concentrations[35]. In a 15-year follow up study, higher levels of CSF Nf-L at baseline were associated with greater disability progression in RRMS patients[36]. Changes in concentrations while on treatment also have been linked to treatment response[37]. Additional markers are being explored actively, but most of the profusion of reports based on studies with smaller populations have later failed replication; Kroksveen and colleagues recently reported that from 188 proposed CSF MS biomarkers, only 10 (5%) have been successfully validated[38].

What needs to be done?

We can summarise these concepts in a vision of what personalised medicine for MS could be: defining the disease suffered by an individual patient in personal, clinical and biological terms that then guide informed decisions on management jointly by the patient and his or her neurologist. These decisions would be based on an evidence base summarized for each patient as a personalised, quantitative estimate of an untreated prognosis and the potential for benefit and harm of different medicines. Decision criteria would be defined based on these estimates and a qualitative appreciation for patient preferences and expectations. Together, this evidence also would provide a solid substrate for cost effectiveness models to support a reasoned debate about how outcomes are valued and healthcare spending is allocated.

We are still far from practicing a truly personalized medicine for MS. Routinely getting the “right drug to the right patient at the right time” will demand coordinated efforts across the MS community. A refocusing of the research agenda is needed. Those involved in MS care, industry, healthcare administrators and patients need to work together to develop:

i. *Large, representative datasets.* Clinical trial data can provide a basis for large datasets shared by the community. Sharing of anonymised, individual subject level data from clinical trials should become the standard. As a pragmatic step towards full transparency of individual data with all clinical trials reports, release of this data with approvals should be required. The academic medical community must lead the way with release of anonymised single subject data with their own reports. These latter data, particularly when well curated and describing real life patient care experience incorporating both clinician- and patient- reported measures will be at the core of future developments for personalised medicine. Many patient characteristics potentially contribute to clinical outcomes; a comprehensive patient profile is needed. As defined in this way, the datasets will be dynamic, growing and evolving in a "learning health system". Creation of these datasets will enable lessons of clinical practice to contribute rapidly to better care.

ii. *Agreement on outcomes meaningful to patients.* The personalisation agenda is predicated on the potential to define health objectives important to the recipient of care, rather than in terms of measures that are clinically convenient or simply easily implemented. This will demand improved capture of the patient experience. Approaches that incorporate data on the environment, lifestyle and employment of individual patients, as well as clinical outcomes, are promising[39].

iii. *Validated models predictive of the behavior of individual patients*. Models that explain data are not enough: to be clinically useful, models also need to be able to predict future outcomes for individuals in a quantitative framework that can provide a basis for joint decision making between a patient and his or her neurologist. Key to this is not just the point estimate of risk, but also an expression of the confidence with which this is estimated. These models need to be dynamic and able to evolve for more accurate and precise risk estimations as new data becomes available. Their principles also need to be transparent and described in ways that allow patients and payers, as well as neurologists, to understand and trust them.

iv. *Decision criteria agreed between all relevant stakeholders.* What levels of outcome prediction are needed to guide changes in management and with what confidence do they need to be

defined? These criteria also must be able to evolve with changes in the way societies and individuals value alternative outcomes, shifting opportunity costs and differences in expectations as new treatment options become available. The principles underpinning these criteria also need to be shared transparently, to encourage dialogue and their use in stimulating innovation in therapeutics. An encouraging new development is work to evaluate the impact of changes in these clinical measures on aspects of life important to patients, such as employment[40]

v. *Enabling of wide access to tools and approaches for personalisation.* Shared best practice across the widest community supports equality of access to medicines and will encourage the most rapid growth in data to improve practice. Harmonisation of assessments and intervention strategies is an important part of data collection actionable for care improvements. Demonstrations of cost effectiveness will be critical to the sustainability of best practice.

Ethical and social considerations

All of the relevant stakeholders- neurologists, patients, industry, regulators and payers- need to be involved in guiding this research and translation agenda if the vision is to be realised. The value propositions for each party are highly interdependent. For example, industry will be unable to drive new drug development with a personalised (or stratified) vision for marketing if regulators do not make it clear that developing the case for a stratified population will be accepted as meaningful or if healthcare payers are not willing to accept the need for the changes needed to enable wide access with individually optimised choices of drugs for MS. Practical clinical use of personalised medicine ultimately will demand that the approaches are cost-effective and accessible.

A key element that cannot be neglected is development of an ongoing dialogue between representatives from all of the stakeholder groups regarding social and ethical issues that arise with personalisation. As trade-offs in public and personal finances always will need to be made, how much does society value ensuring the health of all of its members? What level of uncertainty regarding possible benefit from a medicine will justify withholding – or not supporting- access for some people? Conversely, what level of confidence in the potential occurrence of a serious adverse will justify withdrawing or restricting use of a medicine? How can these decisions be made fairly and reviewed regularly?

Personalised care for MS is not something than can come overnight, although first steps can be taken immediately. Data are still limited and, although models could be built rapidly, ways of incorporating their prospective validation into clinical care are needed. Intentions behind decisions now being made in drug development may not be realized for 1-2 decades. Regulatory shifts must be made cautiously, with a continued concern for unforeseen consequences in vigilance. Thus, to move forward, stakeholders need to develop a long term, joint commitment. Focused dialogue leading towards action is needed now if we are to work pro-actively to ensure the best care for people with MS in medical systems that all are experiencing ever increasing pressures to deliver more for all.

Conclusions

Understanding the heterogeneity of the MS syndrome involves an active process of 'deconstruction' to define the biologically distinct diseases included within it and their interactions with individual, patient specific factors. Coordinated collection and sharing of data, development of predictive models and their progressive evaluation in the care of individual patients will be an essential part of this. At the same time, a much broader range of data on patients will be needed. We should look towards a near future in which care for patients is supported by a comprehensive medical profile including not just clinical data, but also that from devices[41] and patient reported outcomes and behavioural, employment and lifestyle data[42]. In some instances- with the consent and involvement of the patient- this may include data reflecting personal expectations or areas of concern drawn from non-traditional sources, such as social media or online search sites.[43] We believe that 'personalisation', if we take its premise as deconstructing the disease heterogeneity to balance benefit and risk optimally in the management of each patient, should be a clinical priority, rather than a clinical ideal. MS care is an area of neurology in which personalised medicine in neurology needs to be championed.

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Figure Captions

Figure 1. (A) A simplified illustration of the potential cost effectiveness of treatment monitoring for routine interferon neutralizing antibody (NAb) testing of MS patients on IFN treatment. The mean cost of relapse treated in the UK National Health System is £3586[44]. The cost of NAb testing is about £50. It was assumed that the NAb test provides an actionable index discriminating potential full efficacy of the IFN treatment from lack of any impact and that patients recognized to have NAb would be switched to another, equally effective disease modifying treatment of similar cost. Recognition of the NAb therefore leads to savings accruing from avoidance of potential relapse costs associated with loss of efficacy of the IFN (change in relapse rates with loss of efficacy x cost of relapse = 0.52 x 3586 = £1864)[45]. The potential savings per test is the product of savings from avoidance of relapse and probability of a positive test (1864 x 0.45 = £840) . (B) A graphical illustration of the dependence of net benefit of any treatment on baseline risk for a patient. The benefit of treatment was assumed to be proportional to the risk of disease progression (relapse). An "ideal treatment"- one in which there is no cost or risk of adverse events- should benefit all patients, with an absolute benefit (measured, e.g., in adjusted quality of life years) that increases with disease risk. However, in practice, treatments also can have a negative impact on patients, either as cost or adverse events. Here, for simplicity, the negative impact is assumed to arise only from adverse effects of treatment and the risk and impact are assumed to be the same for all patients. Estimation of the *net* benefit to a patient includes consideration both of the impact of treatment to reduce disease activity and the impact of adverse events associated with medicine use. While patients with higher baseline risk from the untreated disease will receive a net benefit (area defined by grid lines to the right), those at lower risk

from their disease may experience net harm (punctate area marked to the left). A goal of personalised medicine is to match the benefit/risk profile of a medicine and the baseline disease risk to optimise the net benefit for a patient.

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