Stratified Medicine: too good to be true?
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Definitions of Stratified Medicine
• “the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a particular treatment” (ABPI White Paper 2009)
• “the potential to use biomarkers for identifying patients that are more likely to benefit or experience an adverse reaction in response to a given therapy” (Trusheim et al, Nature Reviews 2007)

“Classic” Example: Gefitinib versus standard treatment in non-small-cell lung cancer (Mok et al, NEJM 2009)
Analysis of progression-free survival
• EGFR mutation positive patients: HR 0.48 (95% CI 0.36 to 0.64)
• EGFR mutation negative patients: HR 2.85 (95% CI 2.05 to 3.98)
• P-value for interaction < 0.001

To patients:
• Better matching of needs to therapeutic benefit
• Reduced likelihood of adverse events
• More rapid access to new and innovative medicines
• Access to broader range of therapies supported by the NHS
To regulatory authorities:
• Greater confidence for earlier/conditional approval
• Greater confidence in the interpretability of pharmacovigilance data
To the pharmaceutical industry:
• Increased differentiation of new therapies from generic therapies
• Earlier approval of new therapies

Example of the use of ACE inhibitors in cardiovascular disease
• 27% RRR for all cause mortality (p=0.002); 3.7% ARR at 12 months.
• 7% RRR for all cause mortality (p=0.02); 0.5% ARR at 5 weeks.
• 20% RRR for composite endpoint (p<0.001); 0.8% ARR for all cause mortality at 4 years.
Polypill …

Example of trials in Head Injury
• Head injury is characterised by great heterogeneity and a long history of ‘failed’ phase III trials
• 2007 NIH Workshop on classification of traumatic brain injury for targeted therapies (Sattman et al, J Neurotrauma 2008)
• Recognised that head injury trials need to be targeted on the basis of prognosis (triage), mechanisms of injury, and mechanisms of action of the therapies under test
• Need much more informative phase II development, but this has been hampered to date by the lack of robust validated surrogate outcome measures
Stages in individualising a treatment decision
• First, the patient needs to be at risk (e.g. of a cardiovascular event or of recurrence of a cancer)
  • If the absolute risk is too low then it will not be possible to justify the “cost” of treatment
  • If the absolute risk is too high then perhaps treatment is futile?
  • Thus we need a well calibrated prognostic model for risk stratification or triage (e.g. one might prescribe a statin if the 10-year Framingham risk is $\geq 20\%$)

Stages in individualising a treatment decision
• Second, the risk must be modifiable
  • In the absence of more specific information, we often assume that over a quite heterogeneous population the RELATIVE risk reduction resulting from an intervention will be rather similar (this is the basis for most late phase trials and for meta-analyses!)
  • We need excellent basic science to identify plausible interactions (on the relative risk reduction scale)
  • We need comprehensive phase II development programmes and ultimately very large phase III trials to confirm such interactions

Stages in individualising a treatment decision
• Third, the potential individualised absolute risk reduction needs to be set against the “cost” of treatment
  • This includes monetary costs but also the risk of adverse effects. Typically the risk of adverse events is assumed to be constant, but this could also be individualised (e.g. we could attempt to model surgical risk or the risk of a GI bleed when taking aspirin)
  • “Cost” can be very complex if we go beyond the individual – widespread use of antibiotics might be of immediate individual benefit but at the societal cost of the emergence of resistant organisms

Stages in individualising a treatment decision
• Finally, the decision of whether or not to treat can be made on the basis of the estimated costs and benefits
  • This might also require individualised utilities for different states of health and for potential adverse events (e.g. different individuals would have different views on the choice between a mutilating operation with wide surgical removal of a tumour and a less radical operation)

Example of such a modelling exercise
• Targeting antiplatelet, antithrombotic and thrombolytic treatment in acute stroke
• Supported by a recently awarded MRC Clinical Scientist Fellowship
• Informed by systematic reviews and secondary analysis of individual patient data from large epidemiological and trial databases
• Involves developing prognostic models for thrombosis and for haemorrhage, and evaluating the impact of such events of the patient’s quality of life

Conclusions
• There is nothing new about “stratified medicine”!
  • Traditionally, and probably with some justification, trialists view major (qualitative) treatment interactions as being inherently implausible
  • It will take very good basic science and well designed phase II development programmes to identify such interactions
  • I am not (yet) convinced that it would make sense to (provisionally) approve a drug on the basis of such evidence
  • We need to be very conscious of the distinction between identifying individuals with very high potential to benefit from treatment and the problem of reducing the population burden of disease