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Editors' view

Chronic disease: when in doubt, consider accrual into a randomized controlled trial (RCT)

J. M. Ritter, Editor-in-Chief British Journal of Clinical Pharmacology

Department of Clinical Pharmacology School of Medicine at Guy's, King's College & St Thomas' Hospitals St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH UK

A colleague tells of sitting in on the clinic of a wise senior physician of the old school. Presenting the notes (a three volume monster) of the next patient to the chief, he was asked: 'Ben, when I see notes like those, what do I think of?' My friend reflected – what pearl was in store? – and came up with 'chronic disease'. As it happens this was not the correct answer; nevertheless chronic diseases, including chronic infectious and immune disorders, represent distinctive therapeutic challenges that have yielded in part to randomised controlled trials (RCTs) and are the focus of this month's 'Editors' View'.

Background

Clinical endpoints, by definition, occur sooner in acute than chronic disease. Penicillin, first administered to Albert Alexander, an Oxford policeman, had an obvious and immediate effect. By contrast, the effect of streptomycin in patients with tuberculosis was less immediate. Consequently, clinical investigators are faced with an uphill struggle in investigating the effects of drugs in chronic disease. This is a challenge to which they have risen impressively, so that paradoxically we now have much better evidence on which to base therapeutic decisions for several chronic diseases than for many acute conditions (especially ones where there is a surgical treatment option). There is however still much to be done in optimising the treatment of chronic disease.

For mild disease large numbers of subjects need to be enrolled into studies to capture sufficient events, especially as effective treatments are accepted into the standard of practice and hence into the background treatment of control subjects. Before initiating such 'leviathan' studies it is crucial to refine the hypothesis to be addressed to its simplest possible form to avoid mounting very expensive studies that laboriously yield negative answers to clinically irrelevant questions. One way to attempt to avoid such disaster is to use a surrogate marker that is a continuous variable (e.g. blood pressure) rather than a quantal one (e.g. stroke) as the primary endpoint in Phase II investigations that define an appropriate dosage regimen for the definitive Phase III trial. This drastically reduces the numbers of subjects required to establish efficacy and should work well provided the pathophysiology of the disorder is understood. Unfortunately, in our present state of knowledge/ignorance, this is seldom the case, and the inadequacy of a seemingly plausible surrogate (e.g. cardiac output in trials of a drug for heart failure, or the frequency of ventricular ectopic beats in trials of anti-dysrhythmic drugs) is only revealed by counterintuitive clinical trial results [1–4]. Conversely, some apparently 'long shot' surrogates have stood up surprisingly well. It is not immediately obvious, for example, why lowering blood pressure should lower the excess risk of thrombotic stroke or of coronary thrombosis in patients with hypertension, yet there is extremely good evidence that it does so [5].

Chronic infectious disease

Streptomycin (discovered by Albert Schatz in 1943 in Selman Waksman's department in New York) has potent anti-mycobacterial activity (superficially a pretty robust surrogate biomarker) and was used clinically to treat tuberculosis in the USA from the time of its discovery. In Britain, Bradford Hill (himself then recently recovered from tuberculosis courtesy of an artificial pneumothorax) proposed a clinical trial – the first of the modern era. This was justified ethically by the limited supply of the drug and by Britain's

post-war penury (we could not afford to buy much of the little streptomycin that was available). Hill argued successfully that it would be unethical not to subject it to clinical trial in these circumstances, and that this unique opportunity would be lost once supply was plentiful. The resulting two MRC trials, vividly described by James LeFanu [6], used random numbers in sealed envelopes and blinded X-ray evaluations as well as survival as endpoints. The first trial included 107 patients randomly allocated to bed rest plus streptomycin as daily monotherapy for four months (intervention group) versus bed rest alone (control group). After six months 28 of the active treatment group had improved markedly and 4 had died, compared with 14 deaths in the control group. However, unexpectedly and devastatingly, after three years 32 of the 55 streptomycin-treated patients had died compared with 35 of the 52 controls – a consequence of natural selection of streptomycin-resistant organisms. Appreciation of streptomycin resistance led to a second clinical trial in which streptomycin was combined with para-amino salicylic acid (PAS). This rapidly vindicated the use of more than one drug to minimize the emergence of drug resistance. The well intentioned and seemingly ethical approach adopted in the USA of giving anti-tuberculous monotherapy based on a highly plausible hypothesis supported by early clinical response would have led to bad individual long term outcomes coupled with widespread streptomycin resistance: we have much for which to thank Bradford Hill.

Other mycobacterial diseases (e.g. leprosy), and parasitic diseases such as filariasis, also unfold over years or decades. Syphilis is the historical prototype of chronic disease. It was named in a 1530 poem by Girolamo Fracastoro ('*Syphilis sive Morbus Gallicus*' – 'Syphilis or the French Disease'). Fracastoro later explained contagious diseases by the concepts of 'seeds' that infect at a distance and of 'fomites' – objects such as nasal tissues that can harbour and transmit disease 'seeds'. The poem tells the story of a shepherd named Syphilis who is punished for insulting Apollo by an outbreak of 'foul sores' that could be washed away only with quicksilver [7]. Mercury remained the mainstay of treatment, despite its toxicity, until Paul Ehrlich's discovery of salvarsan ('compound 606') ushered in the twentieth century's transformation of therapeutics with its proof of his concept of selective toxicity (the 'magic bullet'). Salvarsan was replaced in its turn by penicillin.

The clinical pharmacology underlying the treatment of syphilis with penicillin is of interest. The causative organism (*Treponema pallidum*) remains highly sensitive, and the drug is extremely non-toxic and well tolerated (unless administered directly into the cerebro-spinal fluid, CSF) so there is no place for therapeutic drug monitoring (TDM). Because penicillin works only on dividing organisms, and because treponemes divide slowly, prolonged exposure to the drug is important. Adherence to prolonged courses of treatment of sexually transmitted disease (STD) is often poor. Consequently, a single dose of benzathine penicillin, a long acting preparation (unlicensed in the UK, but widely used for this indication) is a rational and effective treatment of early syphilis. Late latent disease (where there are fewer organisms that divide even less rapidly) requires a repeat injection after a week. Neuro-syphilis requires prolonged treatment with repeated doses of short-acting penicillin administered parenterally in sufficient dose to maintain treponemocidal concentrations in the CSF for sufficient time to 'catch' organisms during division despite their long doubling time.

The sixteenth century syphilis threat led Henry VIII to close bathhouses and brothels; many believed that the ravages of STD (not just on the individual but also on the next generation via congenital syphilis) reflected divine retribution – an attitude that resurfaced in the twentieth century with the emergence of AIDS [7]. Effective treatment of HIV infection by highly active anti-retroviral therapy (HAART), is one of the triumphs of late twentieth century therapeutics, and was developed via a series of RCTs (in contrast to the use of penicillin for syphilis, which depended on observation versus clinical expectation). HAART has, thankfully, been developed very much more rapidly than the four centuries it took to learn how to treat syphilis adequately, and we are now armed with a range of effective anti-viral drugs that, used in combination, have transformed the outlook for patients infected with HIV. We are still uncertain as to the optimum utilisation of such drugs however. One controversial area is the place of TDM in pregnant patients. Anti-viral effects of non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) are related to their plasma concentrations, and achieved concentrations vary markedly between individuals, so TDM could be useful and has been recommended when starting or changing treatment, and when non-adherence or drug interactions [8] are suspected. However, evidence of improved clinical outcome through use of TDM is lacking and it is expensive. Mother to child transmission is the main cause of HIV infection in children (>500,000 infected per year world-wide). Such transmission can be massively reduced by HAART (currently widely available, sadly, only in richer countries). Pregnancy is associated with major changes in all aspects (absorption, distribution, metabolism and excretion) of pharmacokinetics (PK), and affects exposure to some (e.g. nevirapine, nelfinavir), though not all, anti-retrovirals. We publish in this issue of the *Journal* a review of PK data for NNRTIs and PIs in pregnant women which we hope will inform the ongoing debate as to the clinical relevance of TDM for these drugs during pregnancy [9].

Immune and rheumatological disease

Rheumatoid arthritis remains enigmatic, with poorly understood pathophysiology, an unpredictable and

chronic course and potentially crippling outcome. Aspirin and more potent non-steroidal anti-inflammatory drugs (NSAIDs) relieve symptoms but do not lower the erythrocyte sedimentation rate (ESR) – a crude surrogate marker of disease activity. For many years NSAIDs were used as first line treatment, but gastric intolerance is common and COX II-selective inhibitors (and possibly also non-selective reversible COX inhibitors) increase the risk of mycardial infarction. Glucocorticoids and a heterogeneous group of 'disease modifying drugs' (DMARDs) have toxicities of their own but do reduce the ESR and also influence favourably clinically meaningful endpoints (radiologically-apparent erosions and clinical scores of disease activity). This has vindicated the optimism that underlay their designation as 'disease modifying': they really do modify the course of the disease as well as lower the ESR. More recently, the discovery and development of biological agents that target tumour necrosis factor (TNF) and its receptor by Ravinder Maini and others [10], rivals HAART as being among the most exciting developments in therapeutics. Combination therapy is proving effective in suppressing disease activity and radiological progression, and current clinical practice favours early use of DMARDs. Potentially beneficial combinations, of which there are very many, are being vigorously investigated by RCTs, and the field is moving rapidly. In this issue Lyudmila Sizova reviews the clinical trials that underpin current approaches to treatment of early rheumatoid arthritis with these drugs [11].

Can we extrapolate from therapeutic successes in rheumatoid arthritis to other immune diseases? TNF antagonists are clearly active in several such disorders but, remembering the lesson of streptomycin, we need to proceed with caution and in the context of properly designed and ethically approved clinical trials. This view is emphasised by a report by Sailler and colleagues of serious adverse events including pneumocystis and other serious infections in 14/37 patients with various such disorders treated 'off label' with rituximab (an anti-CD20 antibody approved for rheumatoid arthritis) [12].

Concluding comments

Where does this leave the physician doing his or her best for their patient with chronic disease? An important starting point is to recognise the fallibility of current fashion. It may seem self evident that aggressive treatment of hyperglycemia in patients with Type 2 diabetes will not only lower HbA1c but also improve outcome, but while writing this commentary I am still digesting the results of two trials, one showing that intensive glucose lowering with insulin is actually associated with excess mortality [13] and the other that intensive glucose lowering based on a slow release sulphonylurea strategy does not influence mortality while reducing nephropathy [14]. Such a surprising dichotomy of outcomes is humbling. Ultimately the only way out of the quandary when trial results deviate is to understand the mechanism by which an effect is accomplished. Once one accepts how limited is our current understanding of so many chronic diseases, the logical conclusion is surely to seek out appropriate high quality RCTs and enrol one's patients into them wherever appropriate. When this is not possible one should follow the best available evidence and err towards conservatism: *'primum non nocere* –first, do no harm'.

So what was it that came to the mind of the wise old physician faced with the three volume set of notes? 'No, Ben: I think of my registrar . . .'

Enjoy the summer sunshine and the cricket!

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