Short-term clinical trials of anti-rheumatoid drugs – an opinion

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The problems

A large number of non-steroidal anti-inflammatory drugs are now available for the treatment of rheumatoid arthritis (RA) but the number of second-line agents or anti-rheumatoid drugs (ARDs) has remained small. The use of the established ARDs arose mainly through serendipity and until recently the pharmaceutical industry has failed to develop new ARDs. One of the major obstacles has been the lack of suitable animal models to mimic human RA sufficiently closely. However, in the last few years ICI came close to marketing clobuzarit (Clozic) but S. K. & F. were the first, and at present only, company to have produced and marketed a compound primarily as an ARD, namely the oral gold preparation, auranofin. There is of course still no therapeutic cure for RA, and although superior ARDs will hopefully be forthcoming, the best that might arise in the foreseeable future may be less toxic ARDs of similar efficacy to those currently available.

Producing a potential new ARD is one problem, but obtaining proof of clinical efficacy and comparability with established ARDs and hence a therapeutic profile which is distinct from NSAIDs is an area ripe with difficulties and pitfalls. ARDs are usually distinguished from NSAIDs by virtue of their slow onset of action, their ability to reduce concentrations of the circulating acute phase proteins, and their ability to suppress symptoms for much longer periods than NSAIDs. ARDs may also be distinguished by their ability to slow down long-term radiological progression, but this is still a debatable point [1]. Nevertheless it is important to realise that these distinctions between NSAIDs and ARDs may be arbitrary. There are some drugs which do not fall neatly into one category or the other and it is possible that very high doses of some NSAIDs could exhibit ARD-like activity.

Clinical trials of ARDs tend to fall into short-term trials (e.g. 4–12 months) and long-term trials (2–5 years). The latter are favoured by those ultimately wishing to investigate whether or not long-term ARD therapy affects the outcome of the disease, while inevitably being forced into considering whether or not there is benefit in terms of improved function, reduction in radiological progression and improvement in overall health status as determined by health assessment questionnaires. Interpretation of such trials is hampered by a high drop-out rate, the large numbers of patients required, the duration of the trial and the expense. However, long-term trials are needed if patients are to receive ARDs for long periods. On the other hand the short-term trials tend to focus their attention on the alleviation of pain and stiffness and improvement in serum biochemistry, haematology and immunology. The latter are generally referred to as process measures, having no intrinsic value for the patient, but nevertheless providing an indication that the drug under investigation is doing more than could be expected from an NSAID. British rheumatologists vary considerably in their judgement of patient prog-
ress and this judgement may differ from their expressed opinions [2]. It is therefore not surprising that the short-term trials vary considerably both in the measurements employed, often being selected as a combination of a few standard measures and the personal favourites of the investigator, and in the strategies used to define responders and non-responders. So, even these shorter trials can be inconclusive and, allowing for patient recruitment, possibly with replacement of drop-outs, completion of data analysis etc., the total duration of a study may still be 1½ to 2 years. Nevertheless, the short-term trial represents an inevitable starting point in the clinical development of a new ARD.

A possible answer

It is clear that the clinical testing of ARDs is an area requiring some clarification and definition if serious, efficient and cost effective advances are to be made in the use of ARDs in the treatment of RA. We have been particularly interested in the use of short-term trials for the investigation of both newly developed compounds and drugs which are currently available for other clinical indications but for which theoretical considerations suggest the possibility of ARD-like action. The latter are of importance because the available ARDs were originally produced for other clinical indications and hence it is possible that other available drugs may have ARD action. Our aim has been to develop a protocol suitable for both these applications which would attempt to answer one particular question namely “Does the drug under investigation exhibit sufficient properties to suggest that it has potential as an ARD?” In other words, what is the most effective and rapid way of gaining useful clues to this question? As a result we have developed a “patient model system” or “human screening system” for new ARDs.

This screen is based on an open clinical trial design with historical controls using 7 clinical and 6 laboratory measurements to investigate efficacy. This allows discrimination between NSAID and ARD activity as previously defined. Assessments are performed monthly during a 24 week treatment period in 15 patients with active disease. Statistically significant improvement in the measurements is then looked for and the mean serial data changes are summarised using a somewhat unconventional correlation approach. If the screen produces a negative result then the dose used should first be reconsidered before further clinical trial work on the drug is curtailed. However, if the screen yields a positive result then formal controlled, randomised trials can be embarked upon with more confidence.

Although this screening system has been described in full elsewhere [3, 4, 5], it is appropriate to comment on the selection of measurements. Any variable used to assess improvement should clearly be abnormal in most, if not all, patients with the disease so that it has the potential to return towards normal during therapy. It is also helpful if a variable is independent of age and sex and has a normally-distributed clearly-defined normal range. In addition the methods should ideally be precise, accurate, reproducible between investigators and inexpensive. The clinical methods should be quick and easy to perform in an out-patient clinic, and methods should not require sophisticated equipment or specialised procedures. Furthermore there is little point in performing several assessments which reflect essentially the same phenomenon or the same aspect of the disease. For example, being interested primarily in disease improvement, it would be pointless to measure a range of acute phase proteins which could all expect to fall during successful treatment. On the other hand it may be advantageous to include measures which are thought not to be related to others in order to increase the sensitivity and discriminatory power of the screen. For example one drug may improve pain and the acute phase response while another might additionally improve stiffness and immunological markers. It may also be inferred that a drug which improves most variables may be having more effect on the disease process than one which merely reduces acute phase proteins, though comparison of ARDs is not the primary purpose of the screen. The precise reasons behind the selection of particular laboratory variables have been detailed elsewhere [3], but the six selected were plasma viscosity, C-reactive protein, IgM, serum histidine, total serum sulphydryl and haemoglobin. The seven clinical measurements include articular index (Ritchie), summated change score, pain score, duration of early morn-