Clinical trials: how to cope with medical needs, ethics and timelines

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Current strategies for the management of rheumatoid arthritis (RA) include control of rheumatoid inflammation as soon and as efficiently as possible, slowing progression of structural damage and restoring patients’ functionality while assuring short- and long-term safety.1,2

Despite the approval of tumour necrosis factor (TNF) inhibitors within the past decade and the development of biological agents with a different mode of action, new drugs are currently being developed with the goal to improve efficacy, reduce side effects or to allow a more convenient application considering the patient’s needs. There is also a clear need for efficacious drugs at lower costs than current biological treatment.

Up to now, randomised and placebo-controlled trials have formed the cornerstone of new drug development. In RA, a typical trial enrolls patients for whom methotrexate (MTX) or other disease-modifying antirheumatic drugs (DMARDs) had previously failed, even though a precise definition of therapeutic failure is missing. Typically, patients undergo a washout period of concomitant DMARD treatment, which almost inevitably leads to a high mean baseline Disease Activity Score (DAS), that would otherwise be considered inadequate with regard to standards of care. Regulatory agencies have often required a duration of the placebo-controlled treatment phase of 24 weeks; however, more recently, trials have allowed escape rules for patients not achieving early improvement at week 16.

In this issue of the Annals of the Rheumatic Diseases, Maarten Boers concludes from his meta-analysis of trials using biological agents in RA that the time for 6-month placebo trials has now passed (see article on page 186).3 His analysis is based on 20 trials including 15 placebo and 18 active control cohorts comprising more than 10 000 patients. For placebo controlled trials, he elegantly demonstrates that ACR20 and ACR50 levels clearly differ already after 3 months and the mean difference between month 3 and 6 was not significant. ACR70 responses required a longer time period and were significantly greater at 6 months. For active control trials (for instance, comparing MTX with a new biological agent in MTX -naïve patients) contrasts were smaller, but ACR20 responses were similar at 3 and 6 months. As a consequence, he concludes that a trial duration of 3 months is sufficient to discriminate between active compound and comparator. A recently published trial defined the ACR20 response at week 14 as a co-primary end point.4

Does this have an impact on the design of future RA trials? Shortening the duration of a trial will most likely decrease costs and encourage companies to develop new innovative compounds. As the subsequent clinical development of most new compounds is based on the outcome of a previous clinical trial, shortening the duration of a clinical trial will probably shorten the overall development period of new drugs. Therefore, access to a new compound is facilitated for patients in need.

Limiting the duration of future clinical trials to 3 months instead of 6 months will allow drugs that do not work to be discarded earlier and drugs that ultimately benefit patients to be proceeded with more rapidly. Moreover, shorter placebo-controlled trials, even with a background of inadequate MTX treatment, will have better compliance with the declaration of Helsinki where it is stated:

“C.32 The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances: - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm.”

Most ethics committees are aware of the progress in antiinflammatory treatment and are reluctant—if they allow it at all—to approve extended placebo-controlled trials where a previously “failed” compound (most often MTX) is continued as background drug. They increasingly request active comparator trials which makes trial design (ie, blinding, costs) more complicated. Another problem to consider is that both the placebo phase and the fixed treatment regimen for a certain period of time may raise ethical concerns as tight control is not feasible.

But is the difference between placebo (or an active comparator) and a new compound all we need to know? The full potential of a new compound may eventually be better reflected by comparing the proportion of patients achieving an ACR70 response or reaching remission as defined by a DAS28 of <2.6 or even more stringent criteria (Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI)). In this regard, a clear distinction between phase 2 and 3 trials seems necessary. Early clinical trials such as the abatacept phase 2A trial may show some efficacy but not yet reveal the full potency of a new compound over time.5

The observation that the proportion of patients with an ACR70 response or remission will increase over a time period of 6 or 12 months or even longer, has been shown in several trials with various biological agents.6-7

Therefore, at least theoretically, a new compound could yield a significant ACR20 and ACR50 response in comparison with placebo, but might not necessarily result in high remission rates at a later time point.

Depending on the mode of action, a trial duration of 3 months will almost inevitably favour a compound with a rapid onset of action. The efficacy of biological agents with a cell-based mode of action, such as rituximab or abatacept, will be potentially underestimated, as these drugs may require up to 16 weeks or longer until clinical improvement is seen.8,9

Is it still an adequate approach to use a drug with a slower onset of action in a patient with active RA? Despite the observation that both abatacept and

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rituximab may require a prolonged time period until a clinical response develops, both drugs have demonstrated significant and increasing efficacy over time combined with a favourable safety profile. REFLEX, comparing rituximab with placebo in patients with RA for whom one or more anti-TNF agents had previously failed, demonstrated the superior efficacy of rituximab in inhibiting structural damage in patients for whom clinical treatment had failed.1 The observation that radiographic progression is halted even in patients for whom clinical treatment has failed, certainly justifies the use of a drug with a slower onset of action in an individual patient.

Slowing structural damage currently is, and will remain, a prime advantage for approval of new compounds for RA. Most clinical trials that include evaluation of the inhibition of radiographic progression (as the “gold standard” for assessing structural damage) have a trial duration of 24 or even 52 weeks and, from the viewpoint of obtaining scientifically significant results, will be placebo-controlled. However, looking at TNF inhibitor results from randomised controlled trials (RAPID-1 and -2) comparing the efficacy of certolizumab with placebo, has recently demonstrated that in patients who withdrew in week 16 (in both the placebo and certolizumab group), a significant inhibition of radiographic progression was seen already at this early time point.10 11

Would this be observed in a similar way in patients who were treated with other cytokine inhibitors or biological agents with a cellular-based mode of action? The failure to show a significant effect on radiographic progression at an early time point may not always reflect the inability of the compound to inhibit structural damage. A recent analysis clearly showed that radiographic progression reflects previous disease activity and this may make interpretation of radiographic data obtained at an early time point potentially difficult.12 Alternatively, new imaging methods such as power ultrasound or MRI might be more suitable to examine the question of inhibition of radiographic progression in patients participating in trials with a shortened trial duration.

Will a shortened trial duration provide us with all the necessary safety information we need? This point should be discussed seriously, as safety of a new compound is at least as important as efficacy.

When new compounds, especially those with a new mode of action, are being developed, data on safety will be derived from different sources—the double-blind phase and long-term extension. The double-blind, placebo-controlled phase gives us the unique opportunity over a time period of usually 6 months to compare adverse and serious adverse events in patients receiving the new compound in comparison with the cohort receiving placebo. If serious side effects occur, and this may well be beyond the 3 months’ time point, this represents a serious obstacle for further development. Shortening trials to 3 months’ duration will eventually result in a different view of the side effect profile of a new compound. This may either be in favour of the new drug (when serious adverse events occur after 3 months) or misleading (when serious adverse events occur early such as infusion reactions and may decrease over time).

A potential new design for phase 2 and 3 trials is proposed by Maarten Boers in another paper, combining a 3-month placebo-controlled period followed by active treatment of the placebo patients with standard treatment (TNF inhibitors for example) and adding a placebo to the patients in the experimental arm. Even though this appears to present an ethically acceptable design, disadvantages of this approach include the greater patient number that is needed as not all placebo patients are switched, and disease activity is likely to be lower after 3 months in comparison with baseline for all patients, therefore making a true head-to head comparison difficult (see article on page 4).13

For drugs with a known mode of action, such as TNF inhibitors, shortening the duration of a clinical trial might be appropriate given, from a mechanistical point of view, a comparable mode of action, and a well-characterised safety profile of the whole class. Therefore, the more rapid development of new TNF inhibitors may lead to compounds that are more cost effective, which is in the interest of society.

For compounds with a new mode of action, potential advantages and disadvantages have to be carefully weighed. It may be uncertain at the beginning of clinical development, how quickly a new compound may produce clinical and radiographic efficacy and how many patients will reach remission over time. The incidence of adverse and serious adverse events is usually given in patient-years of exposure. Therefore, treating a large number of patients over a short period of time will not necessarily reflect the same safety profile as for a smaller number of patients but a longer time of exposure.

This meta-analysis by Maarten Boers will certainly stimulate discussions about how clinical trials may best be performed. Finally, the situation of patients with active disease who receive placebo is a major argument for shortening the placebo phase of a trial. Taken together, the current strategy of conducting trials with the possibility for patients to escape at an early time point (might this be reduced to 3 months?) is reinforced by this meta-analysis.

It may be helpful to differentiate between evaluation of a new biological agent within a class of well-characterised biological agents and a compound with a new mode of action and to discuss the demands within a planned clinical trial with doctors, sponsor and regulatory agencies, while, of course, dealing with the patients’ needs.

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