Methodology of combination trials

M. Boers

Department of Clinical Epidemiology & Biostatistics, University Hospital Vrije Universiteit, Amsterdam, The Netherlands

Abstract. Even with the limited number of antirheumatic agents available, theoretical considerations lead to an almost infinite number of combination strategies. This article outlines possible strategies based on the primary choice between maximization of efficacy or minimization of toxicity. Strategies are illustrated with examples from trial experience in the field of rheumatoid arthritis.

Introduction

Combination therapy is becoming increasingly popular in the treatment of autoimmune diseases. This is a direct result of our modest successes in treating afflicted patients, and our ignorance of the etiology and pathophysiology of these diseases. Specifically in the case of rheumatoid arthritis (RA) physicians have become disenchanted with the classical "pyramidal" approach to therapy, i.e., to start with nonsteroidal anti-inflammatory drugs and progress to increasingly toxic antirheumatic agents in case of insufficient response. Surveys have indicated that many rheumatologists are now routinely using combinations [6] even though the evidence for their efficacy is mostly very tenuous [9]. The most popular strategy is that of "step-up", i.e., adding a second (or third) drug in case of insufficient response. The purpose of this article is to outline the theoretical considerations involved in combination strategies, and to explain strategies in use with examples from the literature on RA.

Objectives of combination therapy

As Fathy and Furst [3] explain elsewhere in this issue, the objective (or rationale) of combination therapy is to achieve a better toxicity/benefit ratio. This ratio is poor for most antirheumatic drugs, resulting in high proportions of drug discontinuation for either lack of effect, toxicity or both. Improving the toxicity/benefit ratio can involve
influencing one or both of the factors in the ratio simultaneously. A rational selection of candidates for combinations should emerge from knowledge of the mechanisms of action, both for efficacy and toxicity. Unfortunately, this knowledge is limited, so that clinical research in this field has mostly been characterized by a "trial and error" approach. The main focus of interest has been the improvement of efficacy, as most trials of combination therapy have used full doses of the drugs studied. It must be stressed, however, that efficacy and toxicity are not independent phenomena: except for severe adverse events, patients are more likely to continue a drug that is causing side effects if they experience true benefit. Anecdotal experience with methotrexate in high doses and data from trials that show clear differences in efficacy between the treatment groups (e.g., the COBRA trial [1]) support this observation.

As an example of combination therapy where the main objective is to reduce toxicity, the case of high-dose corticosteroid therapy for autoimmune diseases can be mentioned. In this setting "steroid-sparing" regimens are routine, where other immunosuppressives such as azathioprine are added to minimize the cumulative corticosteroid dose. In the case of cyclosporin A full antirheumatic dosing is not possible due to prohibitive renal toxicity; the drug is now increasingly popular in lower doses in combination strategies, especially with methotrexate.

Theoretical considerations

To understand the possible effects of combination therapies compared with single drug strategies it is easiest to invoke a metabolic model. In this model enzymes produce compounds from raw material (Fig 1). One compound (D) could be equated with disease processes, another (N) with normal physiological processes. Stimulating enzymes that produce N should have a beneficial result, whereas stimulating enzymes that produce D would lead to exacerbation of disease and side effects. The selectivity of a drug is determined by the overlap between the enzyme pathways, and the number of pathways affected by the drug.

Adding a second drug (let alone a third or more) makes the equation considerably more complex. Both for efficacy and toxicity, the second drug can target the same enzyme, the same pathway but a different enzyme, or a different enzyme. The result can be an addition, competition or synergy of the effects, of the single drug (Fig. 2). In the case of addition, the effect of the combination is exactly the sum of the effects of the single components. In the model this is the case where two drugs each target a different pathway (Fig. 3). In the case of competition the effect of the combination is less than addition, and could theoretically even be less than that of the single component. In the model, this can be the case when two drugs target the same enzyme: each drug separately causes partial stimulation (e.g. 75%), but combining the two cannot result in more than 100% stimulation (Fig. 3). A well-known example from microbiology is the combination of some bacteriostatic and bactericidal drugs: the first stops replication of the organism. If the second drug works only on replicating cells, its effect in combination with the first will be negligible. In the case of synergy, the effect of the combination is more than addition. In the model, this can be the case where two drugs target the same pathway but different enzymes, where each separate enzyme cannot be stimulated completely (Fig. 3). An example (but with inhibition instead of stimulation) is the synergistic effect of sulfamethisoxazole and trimethoprim – both inhibitors of different enzymes in the folic acid synthesis pathway – in