Pyramids to myriads: The combination conundrum in rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis continues to be a cause of significant morbidity and disability. Increased understanding of the immunopathogenesis of the disease, of its progression over time, and of patient characteristics which correlate with outcome, have allowed more appropriate therapy. However, currently available disease-modifying therapy fails to adequately control disease in many patients, and many combinations of these drugs have therefore been described. In this review, we critically evaluate the existing literature, identifying combinations for which reasonable evidence of efficacy exists, and highlighting important issues in interpreting such evidence as well as issues of drug monitoring in such patients.

Introduction

Rheumatoid arthritis (RA) is increasingly recognised as a cause of significant disability and morbidity, with mortality comparable to that of three-vessel coronary artery disease or stage IV Hodgkin's lymphoma (1). Information from the Norfolk Arthritis Register (NOAR), a large prospective population-based survey of arthritis, has shown that within the first year, 14.4% of newly diagnosed patients with RA have ceased work. This figure rises to 30.6% (compared with 2.6% in a control population) over a mean follow up of 41 months (2). Recognition of the impact of RA on health has led to earlier and more aggressive therapy (3), research leading to new biologic and immunomodulatory therapies, and much debate as to the best strategies to apply. As a result, the conventional "pyramid" has been inverted (4) and re-invented (5), while others identify new paradigms such as "stepping-up" and "saw-toothing" (6). This therapeutic conundrum requires careful study to make the most appropriate choices for our patients.

Pathogenesis of RA

Our understanding of the immunopathogenesis of RA continues to expand (7), with improved understanding of the role of T cells (8) and other cells in the inflammatory infiltrate (9, 10), as well as of leucocyte adhesion to endothelial cells (11), and definition of the actions of cytokines (12). Monocyte infiltration (13), matrix metalloproteinase and cathepsin production (14, 15), and osteoclast activity (16) all may play a part in the erosion of cartilage and bone, resulting in the deformity and loss of function which characterise this disease. Markers of active disease are now well established, the most valuable being the C-reactive protein (CRP) (17). Novel therapeutic strategies have been identified with mixed results (18), primarily directed at cytokines and their receptors. The more recent inhibitors of tumour necrosis factor α (TNFα) show promise (19). There is also increased, albeit still incomplete, understanding of the mechanisms of action of drugs already known to be effective in RA (20). In the context of combination therapy, the hope would be to identify drugs which will act synergistically without overlapping and/or without interaction of adverse effects.

When to treat - A window of opportunity

There is convincing evidence that RA is at its most aggressive, but also most responsive to disease-modifying therapy, in the first two years. Brook and Corbett (21) have shown that almost 70% of RA patients develop erosions, with 90% of those occurring in the first two years. Indeed, more sensitive imaging modalities such as magnetic resonance imaging (MRI) detect erosions within 4 months in RA (22). The rate of radiological progression may be significantly higher in the first year (23, 24), although this depends to some extent on the scoring method used (25).

When function is assessed, for example, with health assessment questionnaires (HAQs), the "window of opportunity" is again apparent. Wolfe and colleagues (26) compared the 5-year follow up of patients treated within 2 years to groups of patients with a disease duration of 2-20 years treated later, and found a significant improvement in the early treatment group compared with the other groups, who then showed continuing functional loss despite (later) treatment. In another study (27), the "area under the curve" (severity over time) for all function and disease process variables was less for early versus delayed therapy in a cohort of patients with early RA prospectively followed for five years.

Juxtarticular and generalised osteoporosis are important early systemic features of RA. Patients with disease for less than six months have higher bone mineral density (BMD) than those with disease of longer duration, and the rate of BMD loss is higher in patients with early RA compared with controls or with patients whose disease is adequately controlled by disease-modifying antirheumatic drugs (DMARDs) (28, 29).

Whom to treat

While most patients do require aggressive second-line therapy, a proportion remain well controlled with antiinflammatory therapy alone, and up to 30% of patients do not develop erosive RA. Can we identify these patients in advance so that only those with potentially progressive disease need be exposed to the risks of the more potent second-line therapies? An algorithm has been developed from the NOAR data allowing the accurate prediction of patients who will develop erosions (30). The variables used are similar to those previously found to have prognostic value (17). Patients with involvement of at least two large joints, a disease duration of 3 months or more, and positive rheumatoid factor (at least 1:80) had an 89% chance of developing erosions. The risk of erosions was also greater in males, though this was not used in the algorithm. The positive predictive value of this algorithm is similar to that associated with having the HLA-DR4 antigen (31), and is more practicable in most clinical settings.

As mentioned above, MRI scanning frequently detects erosive disease sooner than conventional radiography (CR), and recently high-resolution ultrasound (HRUS) was found to be intermediate in sensitivity between CR and MRI (32). It is unclear whether tests must identify all erosions, or simply find any erosion in a particular patient to identify that patient's disease as "erosive" and indicate appropriate treatment. Therefore, the role for earlier use of these more sensitive imaging modalities is not yet established, and only CR is currently included in the American College of Rheumatology criteria for RA (33).

Combination therapy

The case for combination therapy is made on several grounds. Firstly, many patients continue to decline, functionally and radiologically, despite treatment with successive single DMARDs (34). However, it would be desirable to maintain any partial response obtained with a tolerated treatment, and combination therapy is therefore a logical step. Secondly, the success of combination therapy in oncology, and more recently for human immunodeficiency virus (HIV) patients, is evident. The remission of RA in a patient treated with combination chemotherapy for acute myelogenous leukemia reported by Roubenoff and colleagues (35) is taken as evidence supporting this strategy. (However, single cytotoxic drugs have also been used to good effect, and it is not clear whether the potency of the drugs, rather than their combination per se, brought about remission in this case.) Nonetheless, whether RA is regarded as an infective process, or as a proliferative disorder of synovial or immune-competent cells, the parallel is striking and supports the early use of combination therapy.

Drug resistance is also encountered in these related fields of medicine, where combination regimens are used to avert this. The multiple drug resistance gene and its product p-glycoprotein 170 (pgp-170), a transmembrane transporter which actively excretes drugs from tumour cells, have been studied in RA (36). Cyclosporin and hydroxychloroquine are found to be competitive inhibitors of pgp-170 (37), although the therapeutic implications of these observations have yet to be established.

What treatment?

There is insufficient knowledge of the mechanisms of action of DMARDs to date to allow an entirely rational selection of DMARD combinations. Early studies with cyclosporin suggested that methotrexate should be stopped for a minimum period before cyclosporin was started, and the combination was discouraged (38), but now these drugs are a well-established combination *(v.inf)*. Similarly, both methotrexate and salazopyrin are known to inhibit folate metabolism, implying increased toxicity without benefit from such a combination. However, this combination has also proved useful, although folate supplementation is usually recommended.

The results of two meta-analyses of efficacy (39) place methotrexate (MTX), intramuscular gold (i.m. gold), and salazopyrin (SZP) on an equal footing, though gold had the highest rate of discontinuation. These drugs were found to be superior to oral gold and to antimalarials. Prednisolone (PRD) was not included in this study. Kirwan (40) showed an early symptomatic benefit and delayed progression of radiographic change with fewer new erosions in a group treated with 7.5 mg PRD, although the role of long-term oral corticosteroids is still contested (41). Cyclosporin A (CYA) is at least as efficacious as the antimalarials and has low toxicity (42). Other studies show delayed radiographic progression (43, 44), an important effect associated with the more potent DMARDs. We have experienced no difficulties in substituting the new micro-emulsion-based formulation of CYA, Neoral, in mono- or in combination therapy [unreported data, (45)].

Fries and collegues (46) devised a toxicity index based on the severity of the adverse drug events or laboratory abnormalities and the frequency of their occurrence. Hydroxycloroquine (HCQ) was the least toxic and oral gold (MYC) the most (diarrhea had a very high weighting in this index), while MTX, penicillamine (DPen) and azathioprine (AZA) were closely grouped. PRD was similarly placed, though longterm conse-

quences such as osteoporosis were likely to have been missed in the relatively short follow-up period (mean 2.6 years). SZP was not included in this study, but the toxicity profiles of MTX and SZP have been shown to be comparable (39). The main group of DMARDs was found to be no more toxic than the commonly used non-steroidal antiinflammatory drugs (NSAIDs).

Drug tolerability is also important. Wolfe (47) found a high rate of drug discontinuation due either to poor tolerability or toxicity. HCQ was withdrawn after a mean of only 20 months, and MYC after 25 months. Exceptions were MTX and oral PRD, with over 50% of patients continuing these drugs for more than 60 months.

Different strategies for combining DMARDs have been proposed. The "step-down bridge" described by Wilske (4) uses PRD initially, and in non-responders 3 further drugs are added to obtain remission. The more toxic drugs are then withdrawn, aiming to maintain control with HCQ alone. In the "step-up" approaches, further DMARDs are added where the existing "anchor" drug fails to achieve predetermined targets. The "saw-tooth" approach (6) changes the DMARD in the event of a patient reaching a predetermined "disability level." Drugs may replace, or be combined with, the drug which has lost efficacy. Both the step-up and saw-tooth strategies include the idea of setting therapeutic targets for each drug so that "failure" is readily identified, thus allowing one to move promptly on to the next step. It is important to recognise that both the combination and the regimen must be applied if we are to follow "evidence-based medicine."

Earlier meta-analyses (38,48,49) painted a gloomy picture of combination regimens. However, data from only a small number of trials were analysed, and in some cases the same data appeared in each meta-analysis, falsely amplifying their significance. Furthermore, there is debate about the acceptability of performing meta-analysis combining the results of trials of different drugs (50). Some recent trials have been more promising (Table I).

MTX, SZP, and HCQ (51)

This is regarded as a landmark study of combination therapy, having been carefully conducted, with adequate numbers of patients receiving each treatment and a two-year follow-up period. This double-blind study randomly assigned 102 patients with a disease duration of 6 - 10 years to the combination of all three drugs, to MTX alone (as the "gold standard" control), or to HCQ and SZP combined. The triple regimen was clearly superior (P = 0.03) in a composite score of early morning stiffness, tender or swollen joint count and the erythrocyte sedimentation rate. A 50% improvement was seen in 77% of the patients in the triple therapy arm, compared with 33% and 40% in the other two groups, respectively.

Three important questions are raised by this study. First, can the results be extrapolated to early RA (i.e., less than 2 years' duration)? O'Dell's cohort is unusual in having patients with a disease duration of 6 - 10 years who had not already discontinued MTX or SZP because of toxicity and/or "failure." In a subsequent, open-label study (52), HCQ and SZP were added in patients with an inadequate (less than 50%) improvement on MTX, and significant improvements were seen, suggesting that this combination is of value even when not used *ab initio*. However, it has not been established for early RA patients whether it is best to start a triple regimen from the outset, or whether SZP and HCQ can be added later (up to 10 years later, reflecting the study cohort) for those inadequately controlled on MTX monotherapy.

Secondly, are both SZP and HCQ required as additions to MTX ? There are no studies adding SZP alone to MTX when the latter has failed, and while HCQ and MTX have been tried in combination, there was no clear advantage to the combination [other than a significant reduction in the number of patients with elevated liver enzymes (53)]. In an open-label, randomised study (54) of 40 patients with an insufficient response to SZP (2 gm/day), the addition of MTX in combination was superior to changing to MTX alone. However, this result must not be over-interpreted. A randomised double-blind study (55) of 105 early RA patients not previously treated with SZP or MTX found no advantage to the combination over either drug alone in a one year follow-up.

In an example of the "step-down" approach (56), a cohort of early RA patients was treated with MTX, SZP and PRD. Although initially significantly better than a control group on SZP alone, this difference was lost on discontinuing the steroid at 28 weeks, and there was no significant deterioration on withdrawal of MTX after 40 weeks.

Thirdly, at what dose should one regard MTX as having "failed"? The mean dose of MTX in O'Dell's blinded study was 16.6 mg in the monotherapy group and 16.4 mg in the triple-therapy group. In the latter, open-label study patients were taking a median dose of 17.5 mg when they were converted to triple therapy. Haagsma's studies (54, 55) used a maximum of 15 mg MTX. Others (57) have found an optimum dose (efficacy vs. tol-

Table I. Summary of combination therapy trials; see text for details.

	MTX	SZP	CYA	HCQ	AZA
MTX	———	Parallel E=; T= (see M + S + H)	Add-on E +; T =	Add-on E=; T= (see M + S + H)	Parallel trial E =; T +
SZP	Add-on E +; T =	———	NRT	(see MTX + SZP + HCQ)	NRT
I.m. Gold	Add-on E +; T =	Add-on E+; T?	Add-on E+; T=	Add-on E +; T+	Add-on E+; T=

Notes: Parallel means both drugs were given simultaneously; in add-on trials, the drug in the first column is the "anchor drug" to which the other was added.
E: efficacy, T: toxicity, (+) increased, (=) unchanged, NRT: no reported trials.

erability) for MTX monotherapy of 18 mg. Since there is considerable variation across individual patients, a useful guide therefore would be to consider combination therapy for most patients when MTX alone in a weekly dose between 15 mg and 20 mg is insufficient, although some patients may tolerate higher doses. One cannot generalise about the use of MTX/SZP/HCQ combinations, and must tailor one's decision, depending on the study which most closely represents the patient in question.

MTX and CYA

Tugwell *et al.* (58) used an add-on approach, randomly assigning 148 patients (mean disease duration 9.8 years) with a partial response to MTX (up to 15 mg/week) to the addition of placebo or CYA (2.5 - 5.0 mg/kg). At 24 weeks, outcome measures including the tender joint count, swollen joint count, and HAQ, were improved by at least 50% in 45% of patients from the combination group, compared to 27% of the controls. This study was extended (59), with a follow up of the original combination group over a total of 48 weeks, in which patients who had been randomly assigned to placebo in the first 24 weeks received CYA in the second 24-week period. The first treatment group maintained their improved control, while the group converted to CYA benefitted to a similar degree as the first group.

One could argue that comparison with placebo in these studies is not clinically relevant since patients with incomplete response to MTX would not be continued on the same treatment, although most patients who take monotherapy with MTX are not in remission and have incomplete responses. There are strong indications and theoretical reasons suggesting the use of this combination earlier in the course of a patient's disease, although further studies are necessary.

Gold therapies

A number of patients with longstanding RA initially well controlled by i.m. gold experience a loss of efficacy of this drug, typically 1 - 10 years after starting it. A number of combinations have been used in patients in whom i.m. gold has some benefit, aiming to maintain this effect while improving control.

MTX and i.m. gold (60): MTX was added to i.m. gold in those with incomplete response. A good response, reduced steroid requirement, and reduced tender joint count, or remission were reported in all patients. A combination of oral gold and MTX was not beneficial (61). While these trialists used their own evidence (62) to show that oral and parenteral gold were comparable, Felson (39) found i.m. gold to be more efficacious than the oral preparation, and i.m. gold is continued considerably longer than oral gold in clinical practice (63). Therefore these two combination studies of gold appear consistent with data concerning monotherapy.

CYA and i.m. gold (64): In an uncontrolled, non-randomised add-on study, 20 patients with partial response to i.m. gold received CYA with improvement in early morning stiffness (from 95% to 74% of cases) and moderate-to-marked improvement seen in both the physician and patient assessments of disease (in 89% and 79% of the patients, respectively). Six patients withdrew from the study, three due to typical CYA toxicity (rising serum creatinine), and only one due to lack of effect. A flare occurred in most patients when CYA was withdrawn at six months, suggesting a true benefit rather than simply a placebo response. However, randomised, controlled studies have not been reported.

HCQ and i.m. gold (65): In this double-blind, randomised controlled study over one year, 52 patients (disease duration less than 5 years) received i.m. gold and HCQ, and 49 patients received i.m. gold and placebo. A statistically non-significant trend toward increased efficacy was found, the authors reporting a 20-25% advantage from the combination on a broad clinical, laboratory, and radiological assessment. Perhaps of clinical significance, the CRP did fall significantly in the combination group, and this is regarded as an important marker of progressive disease. However, there was also a trend to increased toxicity, with half of the combination group withdrawing due to adverse effects (mainly rash). Of note, 17 of the 49 controls also withdrew due to adverse effects, rash again being the most common. Conversely, a small study of this combination (but with gold added to previous HCQ), reported only in abstract form, showed improved response in 8 of 10 patients, with no increased toxicity (66).

AZA has been added to i.m. gold but is only described in a textbook. On this combination, 47% of patients were well controlled with no increase in toxicity, but there was no clear comparison before and after combination therapy, or with a control group (67).

MTX and AZA (68, 69): These studies reported the initial 24-week and later, 48-week results of a randomised study comparing either drug alone to the combination. Three different dosage "levels" were used, the maximum dose of MTX being 15 mg/week as monotherapy, but only 7.5 mg/week in the combination arms. The AZA dosage ranged from 50 mg/day to 150 mg/day. More patients on combination drugs discontinued treatment due to adverse effects, without any benefit of increased efficacy. Furst (70), arguing for the rational selection of combinations, has suggested that this combination is unlikely to be of additive benefit.

Overview of combination DMARD therapy

This overview does not purport to be an exhaustive summary of all combination studies. We have instead concentrated on those which appear to be of most relevance to contemporary practice. The results from the trials discussed are sometimes at variance. This may be explained by differences in the patient populations studied, by the evidence previously outlined that RA may behave quite differently in the early and chronic stages, and by the fact that "step-down," "parallel," and "add-on" strategies cannot be directly compared.

We feel that combinations of MTX/CYA or SZP/MTX in those patients who are inadequately controlled on monotherapy (with MTX or SZP, respectively) are well supported by trial literature. The addition of SZP and HCQ to partially effective MTX is another useful strategy. In patients already on i.m. gold with partial effect, the addition of MTX or CYA seems promising. The triple regimen of MTZ, SZP, and HCQ at initiation of

treatment is an important consideration, though its application to a group of early RA patients has not yet been demonstrated.

The role of PRD in combination with other DMARDs is difficult to assess from the current literature. It does seem to be of value in achieving rapid symptomatic relief, and may slow the progression of erosions pending the action of the slower-acting DMARDs (35). A similar role has recently been described for adjunctive intraarticular corticosteroid in early RA patients commencing MTX (71). In general, when patients present with early disease we use the depot (i.m.) injection of methylprednisolone while awaiting the effect of DMARDs, and this appears to be very effective in the short term (unpublished data). In effect it mimics the step-down approach, though not exactly replicating Boers's study (56).

Most of the new biological agents are still undergoing trials as monotherapies to establish their efficacies, although combinations of these agents have been discussed (72). AZA and mycophenolate mofetil have been used in combination in acute graft rejection (73). More relevantly, preliminary reports indicate that combinations of MTX with anti-TNFα therapy are of benefit (74, 75), and a theoretical synergistic role has been proposed (19).

Monitoring patients on combination therapy

The majority of clinical trials showing benefit from combinations have also found little additional adverse effects from an interaction between the various drugs. Some combinations have predictable interactions - for example, MTX relies (70%+) on renal excretion. Where this is reduced by CYA, potential toxicity could be anticipated. Nonetheless, the combination was as well tolerated as the individual drugs (58, 59). While MTX and SZP are both antifolate drugs, no particular adverse consequence was seen in the combination (in either the parallel or the add-on trials), although it would appear prudent to add folic acid in these patients. It has been shown that the addition of up to 25 mg of folate does not reduce the efficacy of MTX as monotherapy (76).

A frequently more important interaction which is often overlooked occurs between NSAIDs and DMARDs. We commonly see raised transaminase levels in patients on NSAIDs, particularly diclofenac, which is of importance when monitoring MTX. Caution is required in the use of NSAIDs in patients taking CYA, and this would be particularly important in those on CYA/MTX combinations. As a rule, the monitoring for combination therapy should be that of the individual drugs. It will be easier in the add-on regimens to identify the likely cause of a new adverse effect, although knowledge of each drug in a combination and their typical toxicity profiles should facilitate appropriate action.

Conclusion

While advances have been made in the treatment of patients with RA, we are still far short of a firm control of the disease in many of our patients. In particular, the evidence of a "window of opportunity" must focus our attention on the aggressive pursuit of optimal control as early as possible. The "pyramid" has been inverted, re-invented, shuffled, and cast aside by various experts, creating instead a "myriad" of therapeutic choices. Combination therapy is one such idea "whose time has come," perhaps borne of desperation, but it is increasingly being recognised as a logical option.

"Diseases desperate grown
By desperate appliance are relieved,
or not at all"

Hamlet

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