Combination DMARD Therapy-Beyond the Data

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The goal of treatment in rheumatoid arthritis is early and rapid control of inflammation as this is thought to improve long-term outcome. However, one is often faced with patients who have tried monotherapy with DMARDs , in whom the usual DMARD combinations have been used and in whom one must try therapies "beyond the data".

In those circumstances, what does one the next?

I would like to suggest the following approach:

a. Look for DMARD combinations with non-overlapping mechanisms of action to improve the likelihood of response;
b. Look for DMARD combinations with non-overlapping kinetics, to decrease the likelihood of negative drug interactions and, consequently, decrease the likelihood of toxicity;
c. Look for DMARD combinations with non-overlapping toxicities to be able to separate the culprit if toxicity does occur.

By looking for DMARD combinations with non-overlapping mechanisms of action, I mean examples such as the combination of leflunomide plus methotrexate. Leflunomide's mechanism of action is probably by inhibition of dihydrorotate dehydrogenase while that of methotrexate is probably through inhibition of aminoimidazocarboxyamide reductase, thus making the combination of these two drugs potentially reasonable, as one affects purine metabolism and the other pyrimidine metabolism. In contrast, the use of methotrexate plus sulfasalazine would not be particularly reasonable as both effect Ig synthesis and, possibly, interleukin-6, thus having overlapping mechanisms of action.

In the area of non overlapping pharmacokinetics, one might look at the combination of cyclosporin A. and methotrexate. Cyclosporin is 94% excreted via the biliary tree while methotrexate's principal mechanism of excretion is through the kidneys. Methotrexate is 70 to 80% renally excreted and up to 30% excreted via the biliary route. While there is some overlap, the differences are great enough so that one could consider these as "non overlapping pharmacokinetics". In a similar vein, leflunomide is 99% protein bound while methotrexate is only approximately 40% protein bound. Again, one can consider these as "non overlapping pharmacokinetics".

Finally, when considering the use of combination DMARDs, one should look for non overlapping toxicities. For example, 10 to 15% of patients given gold sodium thiomalate get skin reactions compared to 3% or less of those receiving hydroxychloroquine. From the toxicity point of view, then, this combination is appropriate as a skin reactions probably due to the gold. Likewise, stomatitis occurs in > 5% of the patients receiving methotrexate and is not part of the toxicity profile for hydroxychloroquine, making it easier to use this combination (Dave Felsen, et al.. Arth Rheum, 1990; 33: 1449).

From a knowledge of these three aspects of the clinical pharmacology of DMARDs, one can develop matrices describing the likelihood of interactions. Figures 1 to 6 demonstrate some of these matrices. Figures 1 and 2, for example, show matrices using methotrexate as the background drug. The next figures show sulfasalazine as the background drug, followed by TNF blocking agents as the background, cyclosporin as the background and hydroxychloroquine as the basic drug. In each case, an "ok" denotes non-overlapping and supports the use of the two DMARDs together; a "-" denotes a negative interaction and does not support the use of the two DMARDs together. A "+/-" implies that it is not clear whether the interaction would be positive or negative, while a "?" denotes a complete lack of knowledge in a given area with respect to the two DMARDs. One of the principal weaknesses of these matrices is the lack of knowledge or lack of in-depth knowledge with respect to drug interactions and it is probably this lack of knowledge that would result in inconsistent or "incorrect" conclusions.

While these matrices are logical, it is appropriate to

Methotrexate Matrix

	Kinetics	Mechanism	Toxicity
Azathioprine	-	-	-(GI,L)
Cyclosporin A	OK	OK	-(GI,R)
D-pen	?	OK	-(R)
Gold	-	+/-	-(R)
HCQ/chloroq.	OK	?	OK

Figure 1.

Methotrexate Matrix(II)

	Kinetics	Mechanism	Toxicity
Leflunomide	OK	OK	-(L,GI)
Minocycline	OK	OK	?
Sulfasalazine	-	OK	-(H,GI)
TNF-α blockers	OK	OK	?
OK-no interaction	?-no data	- potentially harmful	+/- theoretical only

Figure 2.

examine the literature to see the extent to which they enable one to reach correct conclusions.

Figures 1 to 2 show the methotrexate matrices. If one looks at the interaction of methotrexate and gold, one would come to the conclusion that these are not appropriate drugs to use together. In 1992, Williams et al. published in article examining the use of auranofin (an oral gold formulation), methotrexate and their combination for one year. In this double-blind, randomized trial, tender joint counts improved approximately 30% and their acid group, 40% in the methotrexate group and approximately 40% in the combination treated group (not statistically different). The same conclusion can be drawn when examining the swollen joint counts. There were, in fact, no statistically significant differences among the treatment groups during this study. Withdrawals because of adverse drug reactions with slightly more common in the combination treated group but, again, not statistically significantly different. The only statistical difference found was that more patients withdrew from the carina and treated group for inefficacy than the from the combination treated patients. (Williams HJ et al.. Arth Rheum 1992; 35: 406.) Another example is that of cyclosporin plus methotrexate, where a combination appears to be appropriate, based on the matrix. Tugwell et al. used a different study design to examine the combination of cyclosporin plus methotrexate (Tugwell P. et al., N Engl J Med 1995; 33:137). On a background of partial response to methotrexate, this group and either cyclosporin or placebo. This study design is more likely to yield a positive response from the combination and did so in this study. Forty-eight percent of patients in the methotrexate plus cyclosporin group achieved an ACR20 response at the end of the study compared to 16% among the methotrexate plus placebo treated patients. X-ray progression, too, favored methotrexate and cyclosporin. The creatinine increased statistically more frequently in the combination treated than in the methotrexate plus placebo treated groups ($p < 0.05$) although the mean increase in creatinine was small (mean creatinine increase of 0.14 mg%). For the methotrexate matrices, then, one might look to other combinations with a reasonable expectation that two "ok's" would support the use of two DMARDs together. Fewer than two "ok's" should make one hesitate, while two "-"s would probably rule against using the combination together.

Figures 3 and 4 refer to the use of sulfasalazine as the background drug. From one of the matrices, one would have expected that sulfasalazine and methotrexate together would not be a particularly efficacious combination. A 1999 study supports this view (Ann Rheum Dis 1999; 58: 530). In that 52-week, double-blind, randomized study, methotrexate (7.5-15 mg weekly) versus sulfasalazine (2-3 g q.d.) versus the combination showed no significant improvement comparing the combination to either drug alone. Fifty-nine percent of the methotrexate treated patients achieved an ACR20 response compared to fifty-nine percent of the sulfasalazine treated patient and 65% of the combination treated group.

Sulfasalazine Matrix

	Kinetics	Mechanism	Toxicity
Azathioprine	?	-	-(GI)
Cyclosporin A	OK	OK	?
D-pen	OK	OK	?
Gold	?	+/-	?
HCQ/chloroq.	OK	OK	OK

Figure 3.

Sulfasalazine Matrix(II)

	Kinetics	Mechanism	Toxicity
Leflunomide	?	OK	-(GI)
Minocycline	?	OK	OK
Methotrexate	-	OK	-(GI,H)
TNF-α blockers	OK	OK	?
OK-no interaction	?-no data	--potentially harmful	+/- theoretical only

Figure 4.

Figure 5 refers to the use of TNF blocking agents as background for other DMARD therapy combinations. Of note in this matrix is the fact that there are a large number of "?"s, making prediction more difficult. Despite this, there is some data supporting the usefulness of this matrix. A recent trial was published in abstract form which compared etanercept (25 mg sq twice-weekly), methotrexate (up to 20 mg weekly) and their combination. There were approximately 225 patients per group in this 52-week, randomized, double-blind study. Interestingly, 42% of the patients had previously used methotrexate. Methotrexate was quite effective, as 75% of patients achieved an ACR20 response. This compared to 76% of those using etanercept (NS) and 85% of patients using the combination ($p < 0.01$). The combination was also significantly more effective in achieving an excellent response (ACR 70 response)--19% of the methotrexate patients, 24% of the etanercept treated patients and 43% of the combination treated group ($p < 0.01$). (Klaresog et al., Ann Rheum Dis 2003; 62 (Supp.): abstract).

Figure 6 uses hydroxychloroquine/chloroquine as the background drug(s). Surprisingly, there is insufficient knowledge about the mechanisms of action and kinetics of antimalarials, so this matrix could be expected to be less conclusive then the others. There is trial comparing chloroquine, methotrexate and their combination, although there were only 34 to 38 patients per group, making this a statistically underpowered study (Ranza R et al., Arth Rheum, 2000; (Supp.): S345 (abstract)). Interestingly, the authors claimed that 100 percent of the combination treated patients achieved an ACR20 response compared to 73% of those receiving 250 mg daily chloroquine and 68% of those receiving 10 mg weekly methotrexate. This result appears to be a trend, although the abstract did not give statistics.

From the above, it appears that these matrices give some reasonable information that can be used to help guide the use of combination DMARDs when data is not available. For example, the methotrexate matrix would predict the use of methotrexate plus azathioprine together would not be advisable while it might be appropriate to use methotrexate plus minocycline together (although rare liver toxicity after minocycline-not noted in this matrix-might give one a moment's pause). For sulfasalazine, one might consider the use of cyclosporin plus sulfasalazine together, when going "beyond the data". Given an "okay", a"-" and a"?" for the combination of leflunomide and sulfasalazine, one would simply not know the answer. A similar dilemma would exist when considering the use of hydroxychloroquine and minocycline together. In these cases, it would be best try the combinations which are advisable before going to those which are questionable or unknown.

TNF-Blockers

	Kinetics	Mechanism	Toxicity
Leflunomide	?	OK	+/- INFECT.
Minocycline	?	OK	OK
Sulfasalazine	?	OK	OK
MTX	?	OK	+/- INFECT.
OK-no interaction	?-no data	- potentially harmful	+/- theoretical only

Figure 5.

Hydroxychloroquine, Chloroquine Matrix(II)

	Kinetics	Mechanism	Toxicity
Methotrexate	OK	+/-	OK
Minocycline	?	OK	?
Sulfasalazine	OK	OK	OK
TNF-α blockers	OK	OK	?
OK-no interaction	?-no data	- potentially harmful	+/- theoretical only

Figure 6.