Pharmacotherapeutic strategies for disease-modifying antirheumatic drug (DMARD) combinations to treat rheumatoid arthritis (RA)

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ABSTRACT

Objective

To provide a rational model for the use of disease-modifying antirheumatic drug (DMARD) combinations in the treatment of rheumatoid arthritis.

Methods

The DMARDs used today were examined for their mechanisms of action, kinetics, and toxicity, and collected into tabular formats for easier comparison. From these tables, matrices of potential positive or negative interfaces among combinations were constructed. Finally, these matrices were used to examine the usefulness of DMARD combinations by comparing them with published data.

Results

When clearly overlapping cells were found with respect to mechanisms of action, kinetics, or toxicity (e.g., methotrexate [MTX] plus azathioprine or MTX plus auranofin) predictions were good. When knowledge in these areas of kinetics and/or mechanisms of action were inadequate, predictions and results were not always consonant (e.g. MTX plus sulfasalazine; D-penicillamine plus hydroxychloroquine).

Conclusions

The approach demonstrated in this paper toward rational combination therapy is logical and can be successful, although its success is circumscribed by our knowledge about the drugs we use. The rational approach to combination therapy demonstrated in this article can: 1) help prevent the use of combinations unlikely to be effective; 2) can point toward directions for useful research; and 3) can even be used when physicians are faced with patients whose needs have exceeded our present scientific knowledge.

Introduction

In the context of the kinetics, toxicity, and mechanisms of action of disease-modifying antirheumatic drugs (DMARDs), and considering our present day understanding of rheumatoid arthritis (RA) pathogenesis, one can construct a framework for rational combination therapy of RA. In this chapter, we will first, very briefly, describe the present knowledge of DMARD mechanisms of action (more fully reviewed in 1, 2, 3). This will be followed by condensed summaries of their pharmacokinetics and major toxicities. These, in turn, will be woven together to develop rational matrices for combining various DMARDs. As it will not be possible to provide a comprehensive review of the data for such an approach, illustrative examples will be used to demonstrate the principles. It will become obvious, as the process proceeds, that the major limitation of this approach is incomplete knowledge about various aspects of the matrices, especially relating to mechanisms of action and pharmacokinetics. This limitation does not, however, abrogate the principles illustrated by the approach. This approach can help to define future studies and can even help clinicians when they must treat patients who have already tried, and failed, combinations whose results have been well documented.

The mechanisms of action of pharmacologic agents used to "modify" RA

(see Table I)

Azathioprine

Azathioprine (AZA), through its effects on 6-thioinosinic and 6-thioguanylic acid, interferes with adenine and guanine ribonucleotide synthesis (1-4). Its main active metabolite is 6-thioinosinic acid, which itself is a metabolite of AZA's principal metabolic product, 6-mercaptopurine (6-MP). These, in turn, lead to a poorly understood reduction in circulating T-lymphocyte numbers (especially $CD8^+$ suppression), mixed lymphocyte reactivity, B cell function (IgM and IgG synthesis) and interleukin-2 (IL-2) secre-

tion. Although both cell proliferation and Ig synthesis require the nucleic acids whose synthesis is inhibited by AZA, the effect of AZA on Ig synthesis seems less than on cell proliferation.

Cyclosporine A

Cyclosporine A (CSA) complexes with cyclophilin (a cytoplasmic housekeeping protein), which then binds calcineurin (an intracellular phosphatase) (2,5,6). This, in turn, regulates gene transcription coding for cytokines, especially IL-2. CSA inhibits T cell interaction with macrophages and decreases IL-2 synthesis and release, and thus inhibits amplification of cellular immune responses. IL-1- and IL-2 receptor production is also inhibited, so that IL-2-dependent cellular functions, such as B cell responses to T-cell dependent antigens, interferon-γ (IFNγ) production and natural killer (NK) cell activity are decreased. T cells which are already activated are not affected. T cell independent functions, such as macrophage response to lymphokines, are not impaired, and B cell responses to T cell-independent antigens are not affected.

D-Penicillamine

D-Penicillamine (D-Pen) modulates the activities of T-lymphocytes, NK cells, monocytes, and macrophages (7). Although the mechanism of action is still uncertain, it seems likely that the drug regulates the immune system through exchange reactions in or on cell surface receptor sulfhydryl groups. Recent data suggest that D-Pen inhibits the DNA-binding of the transcription factor AP-1, a dimer of the proto-oncogenes *jun* and *fos* (8). This, in turn, reduces the expression of various cytokines, metalloproteases, and cell adhesion molecules, and could account for this drug's antiinflammatory properties.

Gold

Gold in the form of injected organic polymeric gold complexes (such as aurothiomalate or aurothioglucose), or oral gold (as auranofin) enters into cells through a sequence of ligand exchange reactions involving sulfhydryl groups on the cell surface. One possible mechanism of action is similar to that of D-Pen - an interaction with the transcription factor AP-1, since AP-1 binding is inhibited by aurothiomalate (7, 9). This results in a cascade of anti-inflammatory effects (10). The cellular actions of injectable gold may relate to the formation of mo-

Table I. Mechanisms of action of DMARDs.

	AZA	Cyclosporin	D-Pen	Gold	HCQ/CQ	Leflun	MTX	Mino	SSZ
T cell inhibition:	+		+				+		+
$CD8^+$	+								
$CD4^+$									
IL-2		+					+		
IL-8						+			
IL-10						+			
Interferon gamma		+							
B cell inhibition:	+								
Ig synthesis	+			+			+		+
Natural killer cell inhibition		+	+/-						
Prostaglandin inhibition									+
Phospholipase A_2									
Macrophage inhibition:			+	+	+		+		
iNOS								+	
TNFα						+			
IL-1		+			+		+		
Antigen processing:					+				
Activator protein-1 activity			+	+		+			
NFκβ		+		+		+			
Polymorphonuclear leukocyte inhibition:									
Phagocytosis				+				+	
Lysosomal enzyme release				+	+				
Chemotaxis							+		
DHODH						+			
AICAR and DHFR							+		
MMPI (collagenase)			+					+	+
Oxygen radical scavenging									+

AICAR: 5-aminoimidazole-carboxamide-ribonucleotide-transformylase; AZA: azathioprine; DHFR: dihydrofolate reductase; DHODH: dihydroorotate dehydrogenase; D-pen: D-penicillamine; Gold: auranofin and organic gold compounds; HCQ: hydroxychloroquine; Ig: immunoglobulin; IL: interleukin; iNOS: inducible nitric oxide synthase; Leflun: Leflunomide; Mino: Minocycline; MMPI: matrix metalloprotease inhibition; MTX: methotrexate; NFκβ: nuclear factor kappa beta; SSZ: sulfasalazine; TNFα: tumor necrosis factor alpha.

nomeric aurocyanide from cyanide released during polymorphonuclear phagocytosis. If aurocyanide is the active metabolite of organic gold, it would be preferentially formed by activated polymorphs and macrophages. Other effects ascribed to gold are the inhibition of: (i) phagocytosis and lysosomal enzyme activity in polymorphonuclear cells (PMN) and monocytes; (ii) macrophage function; (iii) HLA class II expression on monocytes; (iv) proliferation of synovial cells, and IL-1-induced proliferation of lymphocytes. Immunoglobulin and rheumatoid factor (RF) levels are also decreased. All of these latter effects either require unrealistically high gold concentrations *in vitro* or may be due to gold-induced disease suppression *in vivo*, and may therefore be secondary effects (9).

Antimalarials

Hydroxychloroquine (HCQ) and chloroquine, known as antimalarials, are supposed to change the functions of the acid vesicular lysosomal system (7, 11, 12). HCQ, about which more is known, accumulates in the acid lysosomes of lymphocytes, macrophages, fibroblasts and polymorphs. By alkalinizing the lysozymes and/or interfering with protease function and release, HCQ may affect the glycosylation of proteins, the digestion of membrane proteins, and the turnover of cell surface receptors (13). Additionally, inhibition of IL-1 release from monocytes and macrophages, trapping of free radicals, inhibition of RNA and DNA synthesis, and inhibition of the antigen-processing ability of monocytes and macrophages might be further mechanisms of action through this same mechanism (14).

Leflunomide

Leflunomide, a new drug for the treatment of RA, acts through its metabolite, A77-1726 (15-17). A77-1726 inhibits dihydroorotate dehydrogenase (DHODH), which leads to decreased levels of rUMP, and p53 activation (18). P53 is a "sensor" molecule and prevents, when activated, progression through the cell cycle, so that stimulated cells arrest in the G_1 phase (19, 20). In addition A77-1726 increases the mRNA level of IL-10 receptors, decreases IL-8 receptor type A mRNA concentrations, and blocks tumor necrosis factor (TNF)-dependent nuclear factor-kappa B activation (21). The latter is a particularly important step in the inflammatory response.

Methotrexate

Methotrexate (MTX) very effectively inhibits 5-aminoimidazole-carboxamide-ribonucleotide-transformylase (AICAR), thus decreasing polymorphonuclear chemotaxis (2, 22). A possible, though less likely, mechanism of action is through the inhibition of dihydrofolate reductase (DHFR). Directly and through its 7-OH metabolite, DHFR inhibition can lead to a lack of purine nucleotides, thereby interfering with the formation of DNA, RNA, and other proteins. MTX and 7-OH-MTX-polyglutamates accumulate in cells, resulting in the inhibition of T-cell and macrophage function. Together with other antiinflammatory effects, such as normalization of IL-2 levels (through an effect on polyamine synthesis) (23), the decrease in IL-1 secretion and the reduction of IgM-RF production, these mechanisms make MTX an effective antiinflammatory compound at the macrophage, T cell, and granulocyte levels.

Minocycline

Minocycline, as a representative of the tetracyclines, has multiple immunomodulating and antiinflammatory effects (24, 25). Which of these effects are important in RA treatment is uncertain, because many of them have been seen only in cell cultures or animal models. Minocycline inhibits metalloproteases such as collagenase (from neutrophils, macrophages, osteoblasts, chondrocytes, epithelial cells, and rheumatoid synoviocytes), which may reduce bone resorption (26). A recent study demonstrated the inhibition of IFN-γ-stimulated inducible nitric oxide synthase (iNOS) in macrophages (27). Furthermore, minocycline decreases PMN phagocytosis, chemotaxis, and migration, decreases monocyte phagocytosis, and inhibits lymphocyte proliferative responses. Reduction of IFNγ, IL-2, and TNFα production in cloned synovial T cells and additional putative affects of minocycline may be due to the chelating activity of minocycline, and have not been shown *in vivo* (28).

Sulfasalazine

Sulfasalazine (SSZ) may suppress immunologic processes in the gastrointestinal tract where concentrations are very high, but its mode of antirheumatic action is still unknown (7, 29). While one primary metabolite, 5-acetylsalicylic acid, is the active drug in inflammatory bowel disease, either sulfapyridine alone or both sulfapyridine and the parent compound act in RA. Potentially important mechanisms include the ability to scavenge proinflammatory reactive oxygen species, to lower prostanoid levels (especially leukotriene B_4 in polymorphs and thromboxane A_2 in platelets), and to reduce the number of circulating activated lymphocytes (30-31). Studies documented effects on collagenase and stromolysin on rabbit chondrocytes *in vitro* (33).

The pharmacokinetics of pharmacologic agents used to "modify" RA

While understanding the mechanisms of drug actions is important, it is equally important to know to what degree, and in what form, a drug reaches the putative targets of therapy (the cells in and around the joints, lung, heart, kidney, gastrointestinal tract, and other target organs of this multisystem disease). Furthermore, the duration of effect, potential organ toxicity, and drug interactions of these medications must be understood to use them most effectively and safely. Many aspects of DMARD pharmacokinetics are not known or cannot be placed conveniently in a table. Table II displays the overall pharmacokinetic estimates for the DMARDs being considered. The drug-by-drug examination below expands these data, where possible.

Azathioprine

AZA is well absorbed and metabolized by way of xanthine oxidase, opening a path to interactions with drugs such as allopurinol. The numbers in Table II may be somewhat misleading, as a great deal of intra-individual variation has been documented for AZA pharmacokinetics. For example, there was a difference as large as 257% in azathioprine AUC for

Table II. Pharmacokinetics of DMARDs.

	Absorption	Clearance	Serum elimination (t1/2)	Volume distribution	Protein binding (%)	Elimination	Metabolism
Azathioprine	0.8 (6-MP)	114 (6-MP) (ml/min/kg)	0.2 - 0.5 hr 1.5 hr (6-MP)	—	30	20 - 45% renal	Liver > renal
Cyclosporine A	0.2 - 0.5 variable	2 - 32 ml/min	3 - 7 hrs	3 - 5 l	87	94% biliary 6% renal	CYP 3A
D-Penicillamine	—	—	1 - 7.5 hrs. (up to 6 days)	57 - 93 l	—	25% renal	Liver
Gold thiomalate	0.95*	—	5 - 12 days	—	94	60 - 90% renal	? dicyanogold
Gold thioglucose	0.95*	—	3 - 27 days (up to 168 days)	—	95	70% renal 30% liver	? dicyanogold
Auranofin	0.15 - 0.25	0.0085 ml/min/kg	15 - 31 days	—	71	15% renal 85% fecal	—
Hydroxychloroquine	0.74	95 ml/min	6 - 40 days	5500 l	16 - 25	16 - 25% renal	Liver
Leflunomide	—	0.25 - 0.32 ml/kg/hr	4 - 28 days 60 - 40 days (active metab.)	12.7 l	“extensive”	90% renal or fecal	Liver
Methotrexate	0.73 (0.25 - 1.00)	80 - 90 ml/min/m^2	8 - 15 hrs.	—	45 - 51	49 - 100% renal 20% biliary	Liver
Minocycline	0.90	“low”	15 - 20 hrs.	—	76	10 - 13% renal	Liver
Sulfasalazine	0.33	—	7.6 hrs. (6 - 17 hrs.)	7.5 l	90	70 - 90% renal	Liver GI

* = Animals; 6-MP = 6-Mercaptopurine; GI = gastrointestinal.

the same individual on two consecutive days in one study (34).

The major pathway for 6-MP metabolism is thiopurine methyltransferase (TPMT), and this enzyme’s genetic polymorphism leads to very low concentrations in 1 of 300 persons. Low TPMT levels, in turn, lead to an increased risk of severe myelosuppression after AZA administration in the affected population (35).

Cyclosporine A

CSA absorption is quite variable, although a new formulation, Neoral®, decreases the variability somewhat. Important interaction occurs with grapefruit juice, whose flavons improve absorption by up to 62% (36, 37).

Because cyclosporin is metabolized through the CYP3A system, and because CYP3A is an important drug-metabolizing enzyme family, multiple drug interactions can and do occur. For example, ketoconazole, fluconazole, and erythromycin inhibit CSA metabolism, while rifampicin and phenytoin induce its metabolism, all through CYP3A (38-40). AZA, probably through another and unknown mechanism, can decrease CSA-AUC by about 50% (41).

Others

While the plasma concentrations of gold have half-lives in terms of days and weeks (see Table II), the total body half-life of intramuscular gold is about one year. One of the reasons for the long body half-life is that gold distributes into the macrophages where it is deposited in lysosomes. Eventually, the lysosomes become packed with gold and are then called “aurosomes” (42-45). Synovial fluid concentrations are about 50% of plasma levels.

HCQ is metabolized through de-alkylation to several metabolites, and these have optically active forms. Recent data indicate a closer relationship with efficacy for one metabolite (Desethyl-HCQ) than for HCQ itself (in preparation, Münster *et al.*).

Leflunomide’s total clearance is markedly enhanced by cholestyramine, with a 40 - 65% increase in clearance after 4 days of 8 gm/tid cholestyramine (46). Data on leflunomide and its active metabolite (the active moiety) is scarce. No interactions of leflunomide with cyclosporine, prednisone, or nonsteroidal anti-inflammatory drugs (NSAIDs) have been found, based on clinical studies but not on published, formal pharmacokinetic studies.

MTX absorption is variable between individuals but consistent within individuals. Bioavailability is the same whether MTX is given as a solution, tablet, subcutaneously, or intramuscularly (47). Food does not affect the bioavailability of MTX (48). Age affects AUC, with higher AUC with increasing age from infancy through adolescence, and there is a significant circadian rhythm for MTX pharmacokinetics (49, 50). While MTX itself accounts for most of this drug’s activity, the 7-OH metabolite, which accumulates to a high degree in cells as a

Table III. Selected toxicities of DMARDs.

	AZA (mg/day)	CSA (mg/kg/day)	D-Pen (mg/day)	Gold (mg/week)	HCQ/CQ (mg/day)	Leflun (mg/day)	MTX (mg/week)	SSZ (mg/day)
Eyes					0.7			
Gastrointestinal tract	9-23	6.0		1.3	3.3	2+	2.1	
Nausea/vomiting	9-23		2.0		1.3		2.1	12.5
Diarrhea				3.9 (oral)		2+		
Hepatic	0-5	1.0				2+	10.3	1.6
Renal		25.0		3.0				
Fever	1-6							1.1
Rash				13.0 (3.2; oral)	3.2			3.8
Stomatitis, gingivitis			1.6	1.8			2.6	
Decreased WBC (leucopenia)	4.27		1.0	1.5			1.	1.1
Proteinuria (leukopenia)			5.0	3.7				
CNS effects, paresthesias		8.0					1+	
Other *		1.4		2.2	1.0	2		1.1

AZA = azathioprine; CSA = cyclosporin A; D-Pen = D-penicillamine; Gold = gold sodium thiomalate and oral gold; HCQ/CQ = hydroxychloroquine/ chloroquine; Leflun = leflunomide; MTX = methotrexate; SSZ = sulfasalazine; WBC = white blood cells; CNS = central nervous system.
* Other: Drug-dependent events, but includes items such as hirsutism, hypertension, hair changes, and miscellaneous effects.

polyglutamate, may add to MTX activity (51). NSAIDs decrease MTX clearance, but the effect on toxicity can easily be monitored and is not substantially different among the various NSAIDs (51).

SSZ is extensively metabolized through acetylation and hydroxylation and is then glucuronidated. Since acetylation and oxidation have genetic polymorphisms, substantial differences in metabolism among individuals can occur (52, 53).

Toxicity

Table III outlines the toxicities found in a number of articles and/or from the package information/insert. Occasional or rare adverse events are not shown.

Rational combinations of DMARDs

By using data from Tables I - III, matrices of DMARD combinations can be developed to examine the interactions of DMARD when used in combination. Three such matrices are displayed as Tables IV through VI, for MTX, CSA and HCQ. The principal limitation(s) of these matrices lie in our limited knowledge of these compounds, particularly in the kinetics and mechanism spheres. Because the tables are limited, one can draw only tentative conclusions from them. In general, when negative interactions abound, combinations should not be used; when [?] (not determined) are frequent, predictions are fraught with uncertainty; when all interfaces are "OK," one would expect a positive interaction. From Table IV one would expect that AZA and MTX, as a combination, would not be effective (there are two [-]), nor would gold and methotrexate (two [-]). The effect of CSA plus MTX or SSZ and MTX would be hard to predict from this table (one "OK," one [-], and one indeterminate/unknown). To some extent, these predictions can be tested, based on published studies.

The negative prediction regarding MTX plus AZA was proven true, as the use of MTX plus AZA yielded no additive or synergistic effects compared with MTX alone (54). In a 24-week double-blind, parallel trial, MTX plus AZA was not better than MTX alone and only minimally better than AZA alone. The 30% response in the swollen joint count (SJC) and the tender joint count (TJC) for the groups were: 44% SJC and 44% TJC for AZA; 66% SJC and 55% TJC for MTX; and 58% SJC and 61% TJC for the combination therapy.

Gold (as auranofin [AUF]) plus MTX would also be predicted to be a poor combination, and a 48-week double-blind trial of AUF, MTX, or the combination also supported that prediction (55). A limitation of this, and most trials, is that the disease duration was long (e.g., 55-74 months in this trial). Using 50% improvement as a response criterion, the SJC and TJC responses for the AUR, MTX, and combination (combo) groups were: 34% SJC and 33% TJC for AUR; 43% SJC and 38% TJC for MTX; and 36% SJC and 39% TJC for the combination. Once again, the prediction seems correct.

An "OK" in 1 of 3 columns and a ? in 1 of 3 columns for MTX and cyclosporin indicates an indeterminate chance of an additive response (Tables IV and V). The best trial of this combination was designed to maximize the likelihood of response, as the double-blind administration of CSA or placebo was added to patients inadequately controlled on background MTX (56). Here MTX treatment is tolerated but not sufficiently effective, and an additional drug is added. If the added drug (in this case, CSA) is effective, one would expect an additional response. At the end of this 6-month, double-blind trial, the combination of MTX and CSA improved the SJC and TJC by 24% and 26%, respectively, over MTX alone. It therefore appears that the combination of MTX plus CSA improved the response to background MTX.

Table IV. Methotrexate matrix.

	Kinetics	Mechanism	Toxicity
Azathioprine	OK	[-]	[-] (GI, L)
Cyclosporine A	?	OK	[-] (GI, R)
D-penicillamine	?	OK	[-] (R)
Gold	[-] (R)	OK	[-] (ST)
Hydroxychloroquine/chloroquine	OK	?	OK
Leflunomide	OK	OK	[-] (L, GI)
Minocycline	OK	OK	?
Sulfasalazine	?	OK	[-] (H, GI)

OK = No overlap; [-] = negative or antagonistic interaction; ? = indeterminate or unknown.

Table V. Cyclosporine A matrix.

	Kinetics	Mechanisms	Toxicity
Azathioprine	OK	OK	OK
D-penicillamine	[-] (R)	OK	[-] (R)
Gold	[-] (R)	OK	[-] (R)
Hydroxychloroquine/chloroquine	OK	OK	OK
Leflunomide	?	OK	[-] (GI)
Methotrexate	OK	OK	[-] (GI, R)
Minocycline	OK	OK	OK
Sulfasalazine	OK	OK	[-] (GI)

OK = No overlap; [-] = negative or antagonistic interaction; ? = indeterminate or unknown.
R = renal; GI = gastrointestinal.

Table VI. Hydroxychloroquine/chloroquine matrix.

	Kinetics	Mechanisms	Toxicity
Azathioprine	OK	OK	OK
Cyclosporine A	OK	OK	OK
D-penicillamine	OK	?	OK
Gold	OK	?	OK
Leflunomide	?	OK	OK
Methotrexate	OK	?	OK
Minocycline	?	OK	OK
Sulfasalazine	?	OK	OK

OK = No overlap; ? = indeterminate or unknown.

In contrast, while the matrix is "indeterminate" for the combination of SSZ and MTX (1 of 3 is "OK," 1 of 3 is [-], respectively and 1 of 3 is "indeterminate/unknown"), just as it was for cyclosporin and MTX, the result here is different. A 24-week, double-blind, 105-patient comparison of SSZ, MTX, or their combination yielded no additive effect (57).

Table VI examines HCQ and other DMARDs. It appears as if HCQ/CQ plus any DMARD has at least a reasonable chance of being effective (at least 2 "OK"). While no large, well-controlled trial of MTX plus HCQ has been published, row 6 indicates a reasonable chance of an additive effect (2 of 3 "OK"). An observational study indicated fewer SGPT elevations for the combination of MTX and HCQ than in MTX patients not using HCQ (5.6% versus 9.3%) without any change in efficacy (58). CQ plus MTX showed additive efficacy in a well-controlled trial (59). On the other hand, D-pen plus HCQ showed no additive efficacy, despite the prediction of a possible positive effect (2 "OKs") (60).

Thus, these matrices are often supported by published data, but this approach has limitations. This is especially true when "indeterminate or unknown" interfaces interfere with the ability to clearly determine likely outcomes or, as in the HCQ matrix, lack of knowledge overwhelms the logic of the approach. For example, in Table IV, consider the combination of SSZ and MTX: kinetic interactions are "indeterminate/unknown," mechanistic interactions are "OK" (non-overlapping), while toxicity has a "negative" overlap. A change in any one of these "interactions," based on new knowledge, would radically change the prediction based on the matrix.

Likewise, the lack of any [-] matrix cells in Table VI may be an oversimplification. The combination of D-pen and HCQ was not positive despite its prediction, while D-pen plus CQ was additive (58, 59). This emphasizes our lack of understanding of the similarities and of differences between CQ and HCQ.

These latter examples demonstrate that the matrices continue to be limited by our lack of knowledge of DMARD kinetics, mechanisms, and toxicities, but they do not invalidate the general approach: rational decisions concerning DMARDs can and should be made based on DMARD clinical pharmacology. Furthermore, when faced with incomplete knowledge, the use of data in matrices such as those shown in Tables IV - VI can still improve our choice of DMARD combinations by at least eliminating obviously poor options (2 [-]) and encouraging the use of the most positive choices (3 "OK"). Although controlled trials remain the standard and must be the final arbiter of the DMARD combinations used, the clinician, when faced with a patient who has tried and "failed" proven combinations, can use the rational approach demonstrated here to improve the probabilities of a positive outcome.

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