Does partial control of inflammation prevent long-term joint damage? Clinical rationale for combination therapy with multiple disease-modifying antirheumatic drugs

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Only a decade ago, combination disease-modifying antirheumatic drug (DMARD) therapy was regarded as an unusual approach to patients with rheumatoid arthritis (RA), reserved for only a few patients with the most severe disease (1-3). At this time, however, almost all rheumatologists use combination DMARD therapy in as many as 24% of patients (4, 5). This shift in the approach to people with RA may be explained in part by three developments over the last decade: accurate description of the natural history of RA; availability of improved DMARDs - most notably methotrexate; and perhaps, above all, recognition that partial control of inflammation likely does not prevent joint damage. These developments are discussed briefly below.

Accurate description of the “natural history” of RA
It is of course not possible to describe the natural history of RA, independent of therapies, for pragmatic and ethical reasons (6). However, early epidemiologic studies had indicated that many people who met criteria for RA had a self-limited process with spontaneous remission and no evidence of disease 3-5 years later (7). This course was thought to reflect the natural history of RA as seen in the clinic. However, most patients with RA seen in clinical settings have “persistent inflammatory symmetrical arthritis” (PISA) (8), or Type III rheumatoid arthritis (9), a progressive disease which has not responded adequately to traditional therapies (10).

It is recognized that patients monitored in rheumatology treatment centers in the 1970s and 1980s generally experienced poor long-term outcomes (11-14), including radiographic progression (15-22), joint deformity (23, 24), functional declines (13, 25-27), work disability (12, 13, 28), joint replacement surgery (29), high costs (30-33), extra-articular disease (34), and premature mortality (14, 24, 35-37). Furthermore, more than 70% of patients who develop radiographic erosions do so within the first two years of disease, a phenomenon first described in 1966 (18, 19, 38, 39). Although control of inflammation may preserve some function even after some damage occurs, medication generally cannot restore a severely damaged joint to a normal state.

Therefore, many rheumatologists at this time advocate a “preventive” strategy of aggressive treatment prior to joint damage in RA (40-44).

Advances in DMARD therapy
DMARDs were once referred to as “remission-inducing,” a term which should no longer be used, as sustained remission is seen in fewer than 2% of patients treated with traditional DMARD monotherapy (45). RA is a disorder of regulation, and as no (traditional or even new) drugs address the dysregulation, it may not be expected that any drug, even new biological agents, will lead to a clinical remission of established RA without requiring ongoing treatment. Nonetheless, continuous treatment with DMARDs does ameliorate the course of RA (46-49), including retardation of radiographic progression (50-53). Furthermore, contemporary DMARDs such as methotrexate, hydroxychloroquine, and sulfasalazine have a considerably greater efficacy/toxicity ratio than traditional agents such as gold salts, penicillamine, and azathioprine (54-56).

Over the last decade, new powerful DMARDs have become available, including cyclosporine A (57, 58), leflunomide (59, 60), etanercept (61), and infliximab (62), all of which have been studied as monotherapy and in combination with methotrexate. Methotrexate emerged as a major advance during the 1990s with long-term effectiveness (63-
fewer long-term toxicities than other available DMARDs, and even than many non-steroidal anti-inflammatory drugs (56). While traditional DMARDs such as injectable gold salts, penicillamine, and azathioprine were discontinued within two years by 80% of patients (generally because of inefficacy, toxicity, or loss of efficacy) (54, 55, 66), methotrexate was continued for over 5 years by more than 50% of patients (54, 55). Nonetheless, sustained remission is unusual even with methotrexate, the most effective DMARD (4, 40-42, 67, 68).

When response to one drug is inadequate in many diseases ranging from hypertension to cancer, multiple agents are used. Few patients with RA are in complete remission, and many, if not most, may be candidates for combination therapy (3, 10, 42).

Partial control of inflammation does not appear to prevent joint damage

Emphasis in RA clinical trials and clinical research has been directed to measures of inflammatory activity, such as joint tenderness, joint swelling, and the erythrocyte sedimentation rate (ESR), over weeks or months. Such measures of inflammation are included in the Core Data Set of measures for use in clinical trials endorsed by professional organizations (69-71). Control of inflammatory activity is regarded as an effective strategy to prevent long-term damage, although relatively few studies are available to assess how completely inflammation must be controlled to prevent long-term joint damage.

The possibility that partial control of inflammation may nonetheless be associated with long-term damage is suggested by reports which document that measures of inflammatory activity may be stable or even somewhat improved over periods of 5-10 years, while patients experience disease progression according to measures of damage (24, 72-74). Hawley and Wolfe (Fig. 1) reported improvement or unchanged joint tenderness scores, grip strength, global severity, morning stiffness, ESR, and hemoglobin, but significant progression of functional disability according to health assessment questionnaire (HAQ) scores (72). Fex et al. reported that values for morning stiffness, pain scores, general health, Ritchie Articular Index for tender joints, HAQ scores, ESR, and hemoglobin were similar to baseline after 5-6 years, while radiographic scores indicated significant progression (73). Mulherin et al. (Fig. 2) reported improvement in morning stiffness, pain scores, grip strength, Ritchie Articular Index, ESR and hemoglobin over 6 years, while radiographic scores indicated progression (74). Callahan et al. (Fig. 3) reported that joint tenderness, swelling, ESR, hemoglobin, morning stiffness, pain and modified HAQ (MHAQ) were unchanged or improved, while scores for joint deformity, radiographic damage, grip strength, and walking time indicated progression (24).

There are two reasons why the set of measured inflammatory activity is insufficient to predict long-term joint damage. First, the possibility that partial control of inflammation according to measures of inflammatory activity in a short-term clinical trial may not be translated into optimal or even clinically adequate long-term effectiveness to prevent joint damage, although further analyses are required to analyze this phenomenon.
Nonetheless, such standards for clinical response (75) as the American College of Rheumatology criteria for a 20% response (ACR 20), which provides greater statistically significant differences than a 50% or 70% response (76), may be reassessed over time as more powerful DMARDs are used earlier in disease and in combination (77).

Taken together, we believe the evidence presented above provides powerful arguments that combination DMARD therapy should be considered in most patients with RA, particularly in early disease prior to extensive joint damage, when drug therapy might prevent long term damage (10, 40-42, 44). We invite the reader to review evidence presented in the ensuing 20 contributions in decisions about whether to use combination DMARDs, including which combinations of which DMARDs in which patients would appear optimal.

Organization of the supplement
This overview of combination DMARD therapy in RA is divided into four sections: (i) Overview of combination DMARD therapy; (ii) Evidence from clinical trials of the superiority of DMARD combinations to monotherapy; (iii) Evidence from clinical studies of the superiority of DMARD combinations to monotherapy; and (iv) Experimental combination DMARD therapy.

Overview of combination DMARD therapy
The first section, “An overview of combination DMARD therapy”, includes seven reports, beginning with this introductory report concerning the “Rationale for combination DMARD therapy” (78). The next paper is a report on “Early developments in combination therapy” by D.L. Scott, S. Farrow, and S.I. Yeo, which summarizes the early literature that indicated no added benefit versus monotherapy to combinations involving traditional DMARDs such as gold and penicillamine (79). This is followed by a brief but comprehensive summary of development of combination DMARD therapy, “Pyramids to myriads: The combination conundrum in rheumatoid arthritis” by D. O’Gradaigh and D.G.I. Scott (80). A contemporary review of the mechanisms of action of modern DMARDs by E. Choy and G. Panayi (81) is followed by description of the rationale for “Pharmacotherapeutic strategies for disease-modifying antirheumatic drug (DMARD) combinations to treat rheumatoid arthritis (RA)” by T. Münster and D.E. Furst (82). New observations concerning the imaging of rheumatoid joints prior to the development of erosions by P.G. Conaghan, D. McGonagle, R. Wakefield, and P. Emery are summarized in “New approaches to imaging of early rheumatoid arthritis” (83). The final introductory chapter, “Methotrexate and emerging therapies”, by J.M. Kremer summarizes the basis for inclusion of methotrexate in most current DMARD combinations (84).

Evidence from clinical trials of the superiority of DMARD combinations to monotherapy
The second section, “Evidence from clinical trials of the superiority of DMARD combinations to monotherapy,” includes summaries of seven major randomized controlled clinical trials which have appeared since 1995 to support the efficacy of combination DMARD therapy versus monotherapy, “Combination treatment of rheumatoid arthritis with cyclosporine and methotrexate,” by C.M. Stein and T. Pincus, summarizes a randomized controlled clinical trial, as well as an extension study of this combination (85). A summary of triple therapy with hydroxychloroquine, sulfasalazine and methotrexate by J.R. O’Dell presents long-term results with this combination therapy (86). “Combination DMARD therapy including corticosteroids in early rheumatoid arthritis” by T.T. Möttönen, P.J. Hannonen, and M. Boers, summarizes two studies of aggressive therapy with corticosteroids and combination DMARDs performed in Finland and The Netherlands (87). Clinical trials of combination DMARDs which have appeared in 1998 and 1999 with newer DMARDs include “Methotrexate and leflunomide combination therapy for patients with active rheumatoid arthritis” by P.J. Mroczkowski, M.E. Weinblatt, and J.M. Kremer (88); “Etanercept and methotrexate combination therapy” by A.D. Bankhurst (89); and “Combination therapy of the chimeric monoclonal anti-tumor necrosis factor α antibody (infliximab) with methotrexate in patients with rheumatoid arthritis” by C. Antoni and J.R. Kalden (90).
Evidence from clinical studies of the superiority of DMARD combinations to monotherapy

The third section reviews “Evidence from clinical studies of the superiority of DMARD combinations to monotherapy.” An analysis of the clinical use of combination DMARDs by rheumatologists and their patients is presented in “Use of combination therapy in the routine care of patients with rheumatoid arthritis: Physician and patient surveys” by D.J. Hawley, F. Wolfe, and T. Pincus (91). Reports of analyses of “Combination DMARD treatment with parenteral gold and methotrexate” by R. Rau (92); “Clinical experience with combination disease-modifying antirheumatic drug therapy with cyclosporine” by K. Johns and G. Littlejohn (93); and “Combination cyclosporine and (hydroxy)chloroquine in rheumatoid arthritis” by B.A.C. Dijkmans, R.B.M. Landewe, B.E.E.M. van den Borne, and F.C. Breedveld (94), present the experience of these clinical investigators with these combination DMARD regimens. A clinical approach presented by Wm. Benson and W. Benson describes efforts to “Aim for remission or ‘personal best’ using combination DMARD therapy with methotrexate and hydroxychloroquine” (95).

Experimental combination DMARD therapy

The fourth and final section, “Experimental combination DMARD therapy,” presents innovative approaches in experimental animals. The paper “TNFα and IL-1β are separate targets in chronic arthritis” by W.B. van den Berg, L.A.B. Joosten, and F.A.J. van de Loo, reviews studies of these combinations in experimental mice (96). Studies of “Combination therapy with DMARDs and biological agents in collagen-induced arthritis” by R.O. Williams, A.-M. Malfait, D.M. Butler, M.J. Walmsley, M. Feldmann, and R.N. Maini, analyzes combination DMARDs as elucidating pathogenetic mechanisms in RA (97). The final chapter, by J.D. Isaacs, A.W. Morgan, and V. Strand, describes innovative “Combination biologic therapy” (98).

We hope that the reader will find these 21 manuscripts challenging, innovative, and stimulating. This an exciting time in the development of new therapies for RA. We thank the individual authors for their excellent contributions, the editorial and production staff at Clinical and Experimental Rheumatology for their skilled and helpful assistance, and Centocor Inc., Hoechst Marion Roussel, Immunex Corporation, Novartis Pharma, Sanofi Synthelabo Canada Inc., and Wyeth-Ayerst Laboratories for generous financial support to make this supplement possible. We and the individual authors welcome comments and critiques from readers through the Journal and direct correspondence.

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