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# Aim for remission or “personal best” using combination DMARD therapy with methotrexate and hydroxychloroquine

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**Key words:** Combination DMARDs,  
methotrexate, plaquenil,  
“Personal Best”, Snapshot™,  
Pincus phenomenon.

## ABSTRACT

*Combination disease-modifying anti-rheumatic drug therapy with methotrexate and hydroxychloroquine has changed the course of rheumatoid arthritis. Better management requires “front of the line” care, effective drug combinations, and a goal of “Personal Best.” The Pincus phenomenon - the discrepancy between subjective satisfaction and objective progression - may be minimized in clinical practice by questionnaires and Snapshot™.*

The statement of Verna Wright that “Clinicians may all too easily spend years writing ‘doing well’ in the notes of a patient who has become progressively crippled before their eyes” appears to depict the course of many RA patients more accurately than certain textbook statements.

Theodore Pincus (1, 2)

Rheumatoid arthritis is the most treatable disability in the western world.

Paul Emery (3)

## Introduction

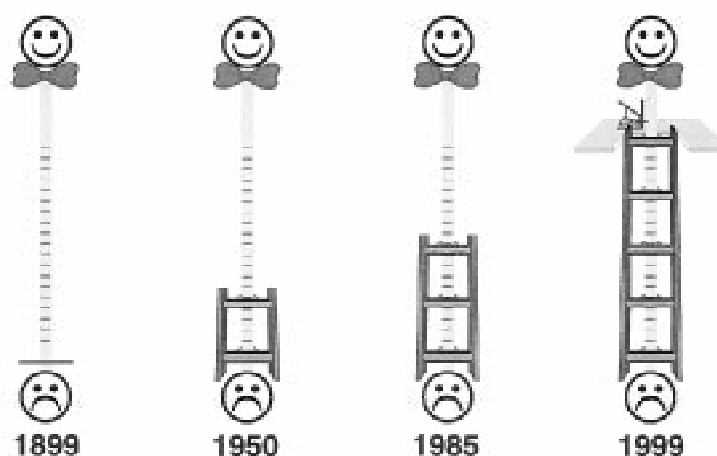
During the past decade, rheumatoid arthritis (RA) has been transformed from a disease of despair to a disease of hope. This transformation is the result of four trends: (i) the widespread use of DMARD (disease modifying antirheumatic drugs), particularly methotrexate (MTX); (ii) the increasing use of combination DMARDs based on MTX; (iii) very early or early-as-possible treatment; and (iv) a goal of remission or personal best for every RA patient.

Although the cure for RA remains elusive, most patients treated in the 1990s can achieve remission or enough control to maintain an acceptable quality of life. It was not always so (Fig. 1). Historically, patients with RA descended at varying rates from good to poor health. By the 1950s, people could take one or two steps towards better health with the help of new drug advances. From the 1970s to the 1980s we had a treatment stepladder. Clinical experience and research has now given us a ladder of treat-

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## Century of Arthritis Management

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**Fig. 1.** Treatment opportunities in arthritis management during the past 100 years.

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## Rheumatoid Arthritis

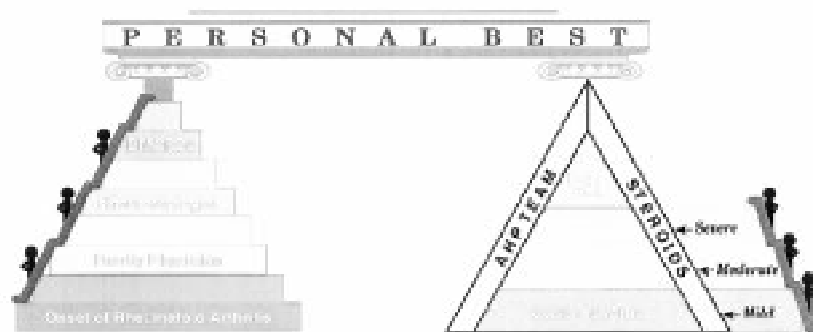


Fig. 2. "Personal best" is achieved by combining a management system with the "step on" treatment.

ment towards a goal of "personal best," not just pain relief.

In this treatment ladder, combination DMARDs are integral to our goal of remission or "personal best" for every patient. This goal can be achieved only through an effective management system and effective therapeutic modalities introduced in a timely manner (Fig. 2).

### The management approach

A little fire is quickly trodden out,  
but being suffered, rivers cannot quench.

William Shakespeare

Recent evidence has clearly demonstrated that the earlier RA treatment begins, the more likely remission is to occur (3). As in cancer or heart disease, timely intervention is essential to the long-term prognosis. The five levels of RA management are shown in the pyramid of Figure 3, with the traditional approach on the left and an escalated approach on the right. If early management of RA is essential, the traditional system makes no sense. It is characterized by delay at all levels such that it is almost too late for remission or "personal best" by the time a patient encounters a rheu-

matologist. Our experience with this traditional approach is that most patients become lost, bewildered, or fall away from medical care, and their rheumatoid disease is never as effectively controlled. In Hamilton, Ontario, Canada in the early 1990s, we developed an escalated approach to ensure that all patients got the care they needed in a timely manner. An essential problem was public awareness. There are prevailing myths about RA, which must be overcome and replaced in the public mind by conscious awareness that treatment of rheumatoid arthritis makes a real difference. RA can conquer you, or you can conquer it. Treatment works, saves dollars, and improves the quality of life, especially when instituted early (4). Patients with RA must, therefore, be brought to the "front of the line." This means that family physicians must be able to recognize the disease and its momentum and make a priority appointment with a rheumatologist. Rheumatologists should see these patients immediately and initiate selective DMARD therapy. Initiating DMARDs early leads to better control in the majority of patients.

### The goal of "personal best"

Ted Pincus made us aware of Verna Wright's description of patients becoming crippled while their doctors noted "doing well" in their charts. Many of us in busy clinical practice are conscious of the urge to be satisfied with current therapy when the patient says "I'm okay," despite ongoing and destructive inflammation. This "Pincus Phenomenon" describes the discrepancy between subjective satisfaction and objective inflammation. If we are going to improve the outcomes of RA, this discrepancy must be challenged and replaced by the goal of "personal best."

Strategically, "personal best" is the pursuit of maximum therapeutic benefit, as quickly and as safely as possible, for all patients diagnosed with RA. While disease remission is possible for some, the end goal for the majority is the sustained control of pain and inflammation and a return to their former quality of life. This is a goal that patients unequivocally embrace, in part because it parallels the now popular homeopathic objective of re-

## Traditional versus Escalated Care

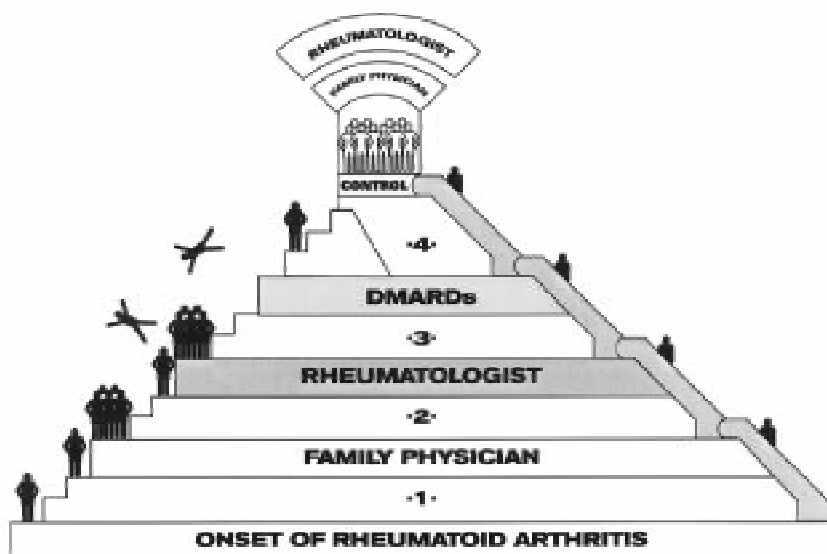


Fig. 3. "Front of the line" (escalated) care is essential for the best outcome in rheumatoid arthritis patients.

gaining or restoring the state of one's health.

"Personal best" means not just pain relief but the best control possible. Currently, we believe there is a wide gap between what most patients achieve and what is achievable. The ladder of treatment seen in Figure 1 is their therapeutic potential. Achieving only part of this potential, while statistically meaningful, is clinically insufficient. The gap between what most patients achieve and what is achievable represents the unresolved therapeutic opportunity.

### Achieving "personal best" in clinical practice

"Personal best", while a lofty ideal, is difficult to quantify and achieve in clinical practice.

Traditional practice falls short - only some of the patients, some of the time achieve disease control. Doctors, nurses and patients are constantly seeking the elusive grail of how to evaluate and summarize improvement in RA. Unlike hypertension or diabetes, RA is too complex and variable to be summarized in a simple number with the treatment to be altered accordingly. This dilemma is compounded by the lack of a common language between doctors and patients - patients and their doctors are often out of sync.

During the past decade questionnaires for disease activity and quality of life have been standardized and validated. These questionnaires give us both a retrospective summary on what has happened and, to those who use them in the clinic, a view of what is happening. Universal adoption of standard questionnaires in all clinical encounters would improve patient care, but we believe that many patients and doctors need an additional or different tool to evaluate and communicate disease and treatment progress.

In Hamilton we use an additional tool called Snapshot™ (Fig. 4) which is a composite of the subjective patient global assessment (from poor to best) and the doctor's objective assessment of inflamed joints. Snapshot™ shows both the doctor and patient where they stand and becomes the common language towards personal best.

The benefits of Snapshot™ are: simplicity; alignment; and relativity and direction. Simplicity is essential for routine clinical use. Alignment between doctor and patient is usual. Malalignment with a positive slope suggests that a patient's perception of the disease is more severe than the objective findings. In our experience many of these patients have co-existent depression and fibromyalgia. A negative slope often indicates that the patient is in denial, simply coping but legitimately unaware of the extent of his or her disease and must be counselled towards a more realistic assessment and approach towards their disease management. Relativity and direction determine

where a patient stands and where a patient must go. We find that the visual image is often more compelling than words alone.

Snapshot™ is not a stand-alone tool but should be combined with both clinical data and standardized questionnaires. We find that when we do not use Snapshot™ we arrive at poorer clinical decisions and outcomes than when we do use it. Snapshot™ encourages hope, treatment change and compliance, and a trend towards continuous improvement and personal best. During the past two years in our clinic Snapshot™ has become the common language interface and has consistently changed our treatment perspec-

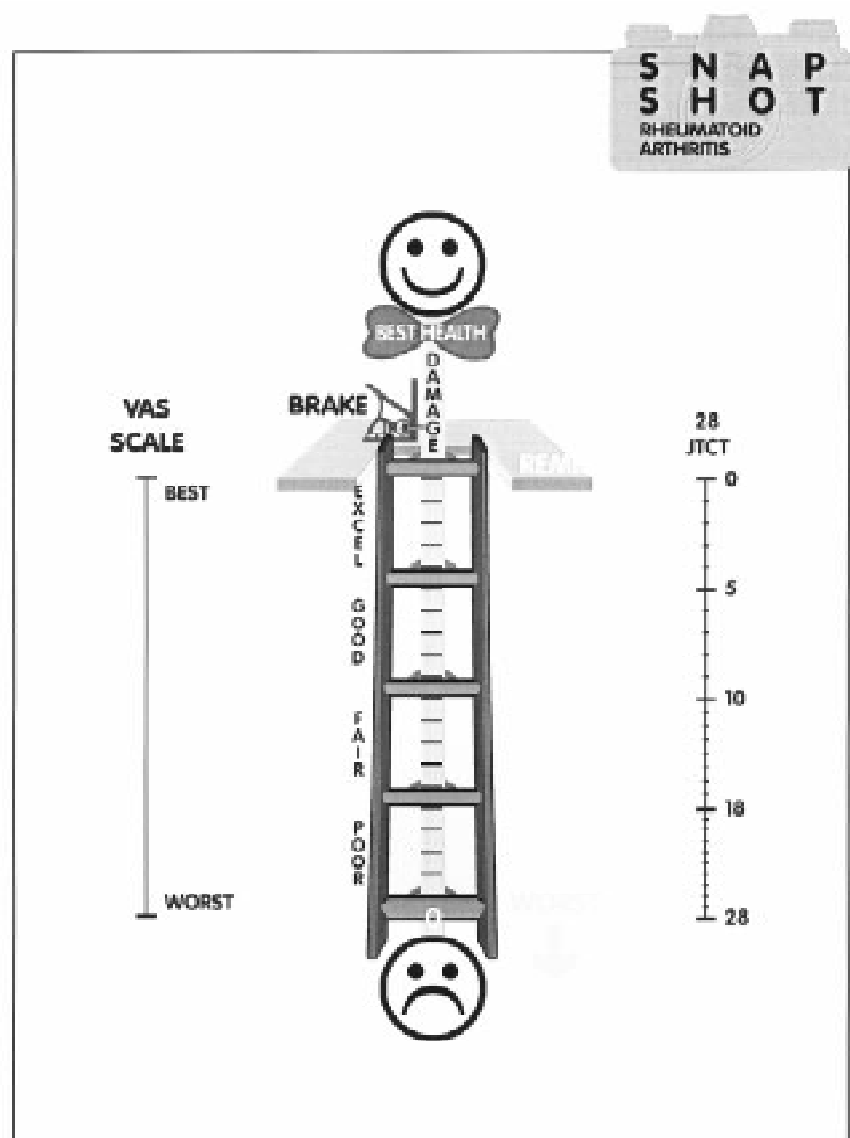


Fig. 4. Snapshot™, a clinical tool to evaluate "Personal Best" and physician/patient concordance.

tive. Further trials and evaluations to validate Snapshot™ will be necessary. Clearly personal best will not be universally achievable in clinical practice without a new paradigm of doctor/patient interaction and disease evaluation.

### Treatment principles of RA

Our approach to RA management is to treat the disease early, aggressively, selectively, and persistently (ASAP). The early, aggressive and persistent approaches are accepted by most rheumatologists, while the selective component remains controversial and will require confirmation through future trials and research. It is this selective component, however, that may be important in determining how and when combination DMARDs should be used.

Currently, the treatment options extend from the traditional "STEP UP" to combination DMARDs when monotherapy with DMARDs fails, to starting everyone on combination DMARDs followed by a "STEP DOWN" after disease control. Both approaches suggest that RA is a homogeneous disease requiring a relatively homogeneous treatment. Most clinical experience and some research suggest, however, that RA has a spectrum of inherent severities or "temperaments" ranging from mild to severe (5). These can be simplified for clinical usage as "mild, moderate, and severe." It is our view that this inherent temperament can be determined with relative accuracy even early in the course of disease by assessing a combination of: (i) the number and severity of joint involvement; (ii) the presence of extra-articular fractures; (iii) laboratory levels of the erythrocyte sedimentation rate (ESR), rheumatoid factor, and HLA typing; and (iv) high resolution ultrasound to determine synovitis and early erosions.

Rather than suggest the same treatment for all, we believe in selective treatment levels for different disease severities. In moderate or severe temperament RA, patients should "STEP ON" to combination DMARDs immediately, and only in mild disease should the initial therapy be mono-DMARDs or antiinflammatory drugs alone (Fig. 2). "Step on" rather than "step up" and/or "step down" saves time and works effectively in a clinical

situation to control disease. A further decade of observations, however, will be required to show whether selective treatment or homogeneous treatment of RA is more successful.

### Combination DMARDs: The Canadian experience

Canadian rheumatologists, through our National RDU and research networks, have aggressively pursued better control of RA. During the past 10 years in Canada, the pendulum has swung from mono-DMARDs to the frequent use of combination DMARDs, both in the "step on" and "step up" formats. At McMaster University, two early pilot studies suggested that cyclosporin A might be useful in combination with both MTX and gold for RA patients who had failed monotherapy (6). Soon after, the HERA study (Hydroxychloroquine in Early RA trial) demonstrated the efficacy and safety of hydroxychloroquine (HCQ) in early RA (7). The HERA follow-up trial suggested a better long-term prognosis in patients treated with HCQ (8). Canadian rheumatologists embraced HCQ as a safe and effective DMARD and wondered if it would be a logical choice for combination with MTX.

The pairing of HCQ and MTX is therapeutically appealing because these drugs are effective individually and possess complementary pharmacologic profiles.

HCQ alone is considered the least toxic of the widely used DMARDs and offers a better toxicity profile than 9 of 10 common nonsteroidal antiinflammatory drugs (NSAIDs) (9). Retinopathy is rare with HCQ at dosages of 6.5 mg/kg/day, so that initial and periodic ophthalmologic exams suffice to simplify the monitoring of this antimalarial (10). Whereas HCQ is initially slower to act, MTX compensates in combination with a rapid onset of action, making MTX a preferred DMARD selection despite the inherently more stringent monitoring it requires.

The combination of MTX plus HCQ has been studied further in two pilot trials published to date only in abstract form. The first trial was a prospective 16-week pilot study of 20 RA patients with a disease duration of less than two years who were treated with "step on" combination therapy with HCQ, MTX and intramuscular (i.m.) methylprednisolone (11). The results (Fig. 5) demonstrated a dramatic improvement in all parameters within 16 weeks except for the ESR, which was surprising to the investigators. HLA sub-typing, performed retrospectively to address concerns that these RA patients may have had mild, relatively non-progressive RA, revealed that 10 patients had no copy of the DR shared epitope for RA (consistent with milder disease), 8 patients had one copy (con-

### Efficacy Outcome Measures: Effect Sizes

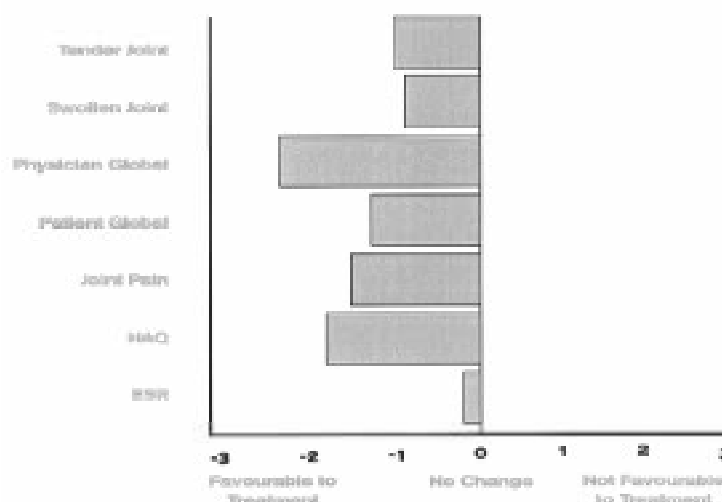


Fig. 5. Efficacy outcome measures in the Canadian "Step On Approach in Early RA" trial.

**Table I.** Efficacy outcome measures.

	Week 0 (mean $\pm$ SD) (n = 20)	Week 16 (mean $\pm$ SD) (n = 20)	Change $\pm$ SD 95% [C.I.]	P value
Tender joint count (0 - 68)	20.7 $\pm$ 12.8 (n = 20)	6.5 $\pm$ 7.6 (n = 20)	-14.3 $\pm$ 3.2 [-20.97, -7.53]	< 0.001
Swollen joint count (0 - 66)	14.7 $\pm$ 10.1 (n = 20)	4.4 $\pm$ 4.7 (n = 20)	-10.3 $\pm$ 2.3 [-15.01, -5.6]	< 0.001
Physician's global evaluation (1 = very good to 5 = very poor)	3.7 $\pm$ 0.75 (n = 20)	1.9 $\pm$ 0.79 (n = 20)	-1.8 $\pm$ 0.25 [-2.27, -1.23]	< 0.001
Patient's global evaluation (1 = very good to 5 = very poor)	3.6 $\pm$ 0.76 (n = 20)	2.1 $\pm$ 1.02 (n = 20)	-1.5 $\pm$ 0.27 [-2.0, -0.88]	< 0.001
Joint Pain	3.5 $\pm$ 0.83 (n = 20)	2.3 $\pm$ 0.73 (n = 20)	-1.2 $\pm$ 0.27 [-1.72, -0.58]	< 0.001
Pain - Visual analog scale (0 = none to 100 = very severe)	61.8 $\pm$ 23.5 (n = 20)	25.8 $\pm$ 23.5 (n = 20)	-35.9 $\pm$ 7.8 [-52.3, -19.6]	< 0.001
Health Assessment Questionnaire (HAQ)	1.7 $\pm$ 0.64 (n = 20)	0.5 $\pm$ 0.57 (n = 20)	-1.2 $\pm$ 0.18 [-1.54, -0.78]	< 0.001
Erythrocyte sedimentation rate (ESR) (Wintrobe)	40.9 $\pm$ 25.3 (n = 20)	35.4 $\pm$ 27.5 (n = 20)	-6.7 $\pm$ 6.4 [-20.0, 6.7]	0.306

sistent with moderate disease), and two patients were homozygous for the shared DR epitope (consistent with severe disease). The clinical features of these patients were related to their HLA subtypes.

The degree of therapeutic response was similar for all patients across the mild, moderate, and severe spectrum. This suggested that combination DMARDs play an important role in patients with moderate or severe temperament RA, for whom traditional therapy often fails to achieve significant clinical improvement. The clinical changes were dramatic. The mean tender joint count fell from 10.7 to 4.7 (68.8%) and the mean swollen joint count from 14.7 to 4.4 (70%). All patients stopped their steroid after the initial doses. The two patients with severe disease at 18 months were still in complete remission. In these two patients very early use of combination DMARDs may have fit into "a window of opportunity" to bring their disease under control (11). However, this was a single arm, non-placebo-controlled, observational study with all the inherent weaknesses of this type of study.

In the second study, 103 patients (age 18 to 80 years) who received HCQ in addition to their existing MTX therapy in

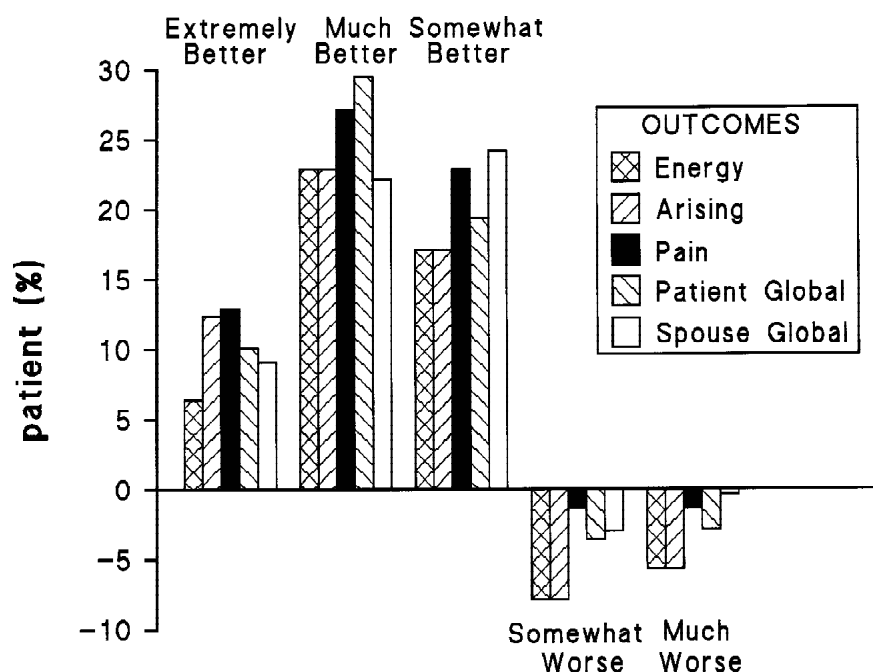
1995 were reviewed by a nurse clinician from October to December 1996. A chart review was completed on these patients and data were collected including the symptom onset time since diagnosis, RF, ESR, joint count, morning stiffness, disease activity, and functional status. Each patient also completed five questionnaires. A modified questionnaire was used to quantify their degree of pain, disease activity, and overall health using a 7-point Likert scale (1 = extremely better and 7 = extremely worse). The second questionnaire reported the d-HAQ variables as being either easier, the same, or harder. Spouses also completed a global assessment (Table I, Fig. 6).

Patients' perceptions of changes that they had experienced in the disease since starting combination therapy are shown in Figure 6. Most patients felt that their pain, morning stiffness, swelling, energy level, and activity level were somewhat better to much better after starting DMARD therapy. The majority of patients reported a large improvement in their overall health. A spousal questionnaire reported slightly less but also substantial improvement in the patients' overall health. Patients were asked to think about d-HAQ activities in terms of their being easier or harder to accomplish

since they had started their combination therapy. The majority of patients found these activities easier to accomplish since starting combination therapy (Fig. 6). These patients had longstanding disease with an average duration of 13 years. They had been satisfied with their current condition. Most had to be persuaded to initiate combination DMARD therapy because they did not believe that further improvement in their disease was possible. The degree of improvement both clinically and statistically surprised both the patients and the doctors and suggested that our clinic had a significant unresolved "Pincus Phenomenon." This study was a retrospective review of the patients' perception of change and had all of the weaknesses inherent with this approach (patient recall, etc). Another limitation was the absence of a control group of patients who were continued on monotherapy alone.

#### Literature review: HCQ + MTX

International support for administering HCQ plus MTX to early RA patients with moderate to severe disease arises from studies which suggest that this DMARD combination offers greater efficacy and opportunities for disease control, with fewer adverse reactions and a



**Fig. 6.** Changes in outcomes since the initiation of combination disease-modifying antirheumatic drug (DMARD) therapy. The chart summarizes the distribution of patient numbers across the Likert scale response categories describing the amount of change after the initiation of therapy.

possible additional benefit compared with monotherapy.

Trnavsky *et al.* reported excellent results in a 6-month, randomized, placebo-controlled study in which 20 RA patients treated with HCQ (200 mg/day) plus placebo improved in only 3 of 6 clinical variables and zero laboratory parameters, while 20 patients treated with HCQ (200 mg/day) plus MTX (7.5 mg/week) tolerated the therapy well and improved in all clinical variables. These variables included the articular index, the number of swollen/effused joints, minutes of morning stiffness, and pain on movement, with significant improvement ( $P = 0.05$ ) in both pain at rest and the Dixon's index. Significantly reduced ESR and circulating immune complex values were unique to the combination group, as was a reduced degree of radiologic disease progression that encourages further examination. (13).

A recent two-part study by Clegg *et al.* (14) confirmed not only that HCQ plus MTX significantly improved both the clinical and laboratory parameters for RA at 6 months, but also that subsequent maintenance with HCQ actually delayed the occurrence of flare ( $P = 0.023$ ). The first segment of this multicentre study was open label and involved treating 141

patients for 24 weeks with HCQ (200 mg bid) plus MTX (7.5 mg/week for 6 weeks, followed by up to 15 mg/week). MTX was then withdrawn, and responders ( $n = 121$ ) continued through a second double-blind, parallel segment of 36 weeks randomly assigned to 1 of 3 groups: (i) HCQ plus MTX as needed for disease flare ( $n = 40$ ); (ii) HCQ 400 mg/day ( $n = 41$ ); or (iii) placebo as needed with MTX for disease flare ( $n = 40$ ). Combination therapy in the first segment of the Clegg *et al.* study was effective and well tolerated, resulting in decreased mean swollen joint scores within all groups ( $P < 0.001$  versus baseline), decreased painful and tender joint scores within all groups ( $P < 0.001$  versus baseline), and improved values for other disease variables except for the duration of morning stiffness, which did not significantly improve in the HCQ group. The only between-group differences in the first segment were that group (iii) candidates tended to have class II or III disease versus class I disease compared with group (ii) ( $P = 0.048$ ), and the difference between groups (iii) and (i) approached statistical significance ( $P = 0.08$ ).

In segment two, the combined flare-free curve for groups (i) and (ii) (who received the same medication until the first

flare) was better than for group (iii) ( $P = 0.023$ ) over the 36 weeks. The first 8 weeks of segment two, however, showed similar flare-free curves for all three groups, especially (i) and (iii). At the end of 36 weeks, among only the patients who had not flared up to week 8, overall flare-free rates were higher for groups (i) (65%) and (ii) (72%) versus group (iii) (27%;  $P < 0.05$ ). Clegg *et al.* thus found HCQ to extend the flare-free duration curve benefits initially accrued from combination therapy with HCQ plus MTX.

An unanticipated, although noteworthy, discovery from combining HCQ with MTX is that it also appears to stabilize hepatic enzymes at normal levels. This may allow patients with elevated enzymes who otherwise respond well to MTX alone to continue receiving therapy. In a review of anti-rheumatic drug therapies used to treat 2600 RA patients enrolled in the multicenter ARAMIS Post-Marketing Surveillance Program, Fries *et al.* (15) found that MTX monotherapy resulted in the highest values for serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT). HCQ alone, however, resulted in the lowest values. The combination of MTX and aspirin further resulted in the highest SGOT and SGPT values, whereas HCQ combined with either MTX or aspirin yielded the lowest values after adjusting for age, sex, and the duration of disease.

A study was carried out in 1998 by Dr. Maria Suarez-Almazor (16) on the prescribing patterns of 25 Canadian rheumatologists choosing to modify DMARD monotherapy in 246 inadequate responders with RA. Dr. Suarez-Almazor found that, at the time of modification, most patients were already receiving MTX alone (39%) or HCQ alone (31%). The most common combination prescribed to the MTX-alone group was HCQ plus MTX (73%). Similarly, patients receiving HCQ were most often prescribed HCQ plus MTX (72%). This represents a definitive shift away from a decade of automatically switching non-responders over to alternative single DMARDs. For obvious reasons, there is a strong leaning toward combination therapy internationally and HCQ plus MTX in particular.

## Summary

During the past decade in Canada, RA has become a disease of hope rather than of despair due largely to the widespread institution of combination DMARDs. MTX combined with HCQ is the most widely used Canadian combination. Two Canadian pilot trials, the Step On Approach in Early RA, and the Step Up Approach in Progressive (13 years RA), both observed efficacy with combination MTX plus HCQ. Two published studies (13, 14) also support increased efficacy with MTX plus HCQ.

To achieve our goal of remission or "personal best" for every patient, we need to modify our management approach and our therapy with combination DMARDs. All RA patients must be brought to the "front of the line" for treatment. Ideally, treatment in patients with moderate or severe temperament disease should start with "step on" combination DMARDs. Patients with progressive (i.e., long-standing) RA often have an unrealized therapeutic opportunity which can be met by "step up" combination DMARDs. This unrealized therapeutic opportunity must be identified at each patient-doctor encounter in our striving for the goal of "personal best." In our hands Snapshot™ (Fig. 5) inserted within our patient assessment sheet (Patient Portrait™) makes it simple and effective to identify where patients stand and where

they need to go in order to achieve their personal best. We believe that Snapshot™ used widely would improve the care of RA patients.

RA is the most treatable disability in the western world. There remains a widespread Pincus Phenomenon, however, i.e., the perception that subjective satisfaction equals objective control, in far too many RA clinics. Combination DMARDs judiciously applied with the ability to measure results should help us to improve the prognosis of this disease.

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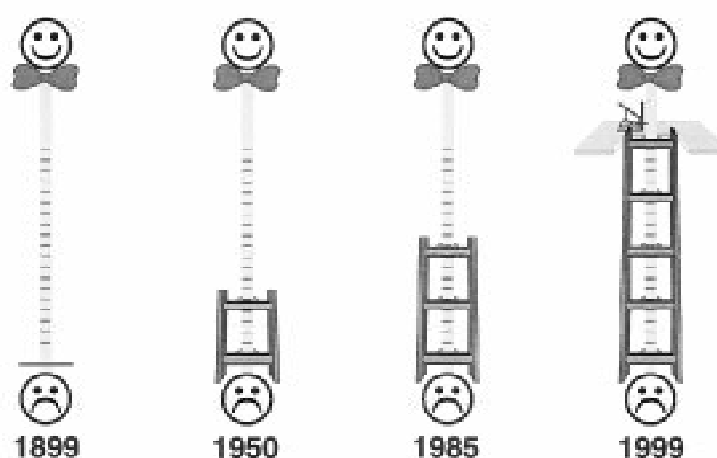
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but being suffered, rivers cannot quench.

William Shakespeare

Recent evidence has clearly demonstrated that the earlier RA treatment begins, the more likely remission is to occur (3). As in cancer or heart disease, timely intervention is essential to the long-term prognosis. The five levels of RA management are shown in the pyramid of Figure 3, with the traditional approach on the left and an escalated approach on the right. If early management of RA is essential, the traditional system makes no sense. It is characterized by delay at all levels such that it is almost too late for remission or "personal best" by the time a patient encounters a rheu-

matologist. Our experience with this traditional approach is that most patients become lost, bewildered, or fall away from medical care, and their rheumatoid disease is never as effectively controlled. In Hamilton, Ontario, Canada in the early 1990s, we developed an escalated approach to ensure that all patients got the care they needed in a timely manner. An essential problem was public awareness. There are prevailing myths about RA, which must be overcome and replaced in the public mind by conscious awareness that treatment of rheumatoid arthritis makes a real difference. RA can conquer you, or you can conquer it. Treatment works, saves dollars, and improves the quality of life, especially when instituted early (4). Patients with RA must, therefore, be brought to the "front of the line." This means that family physicians must be able to recognize the disease and its momentum and make a priority appointment with a rheumatologist. Rheumatologists should see these patients immediately and initiate selective DMARD therapy. Initiating DMARDs early leads to better control in the majority of patients.

### The goal of "personal best"

Ted Pincus made us aware of Verna Wright's description of patients becoming crippled while their doctors noted "doing well" in their charts. Many of us in busy clinical practice are conscious of the urge to be satisfied with current therapy when the patient says "I'm okay," despite ongoing and destructive inflammation. This "Pincus Phenomenon" describes the discrepancy between subjective satisfaction and objective inflammation. If we are going to improve the outcomes of RA, this discrepancy must be challenged and replaced by the goal of "personal best."

Strategically, "personal best" is the pursuit of maximum therapeutic benefit, as quickly and as safely as possible, for all patients diagnosed with RA. While disease remission is possible for some, the end goal for the majority is the sustained control of pain and inflammation and a return to their former quality of life. This is a goal that patients unequivocally embrace, in part because it parallels the now popular homeopathic objective of re-

## Traditional versus Escalated Care

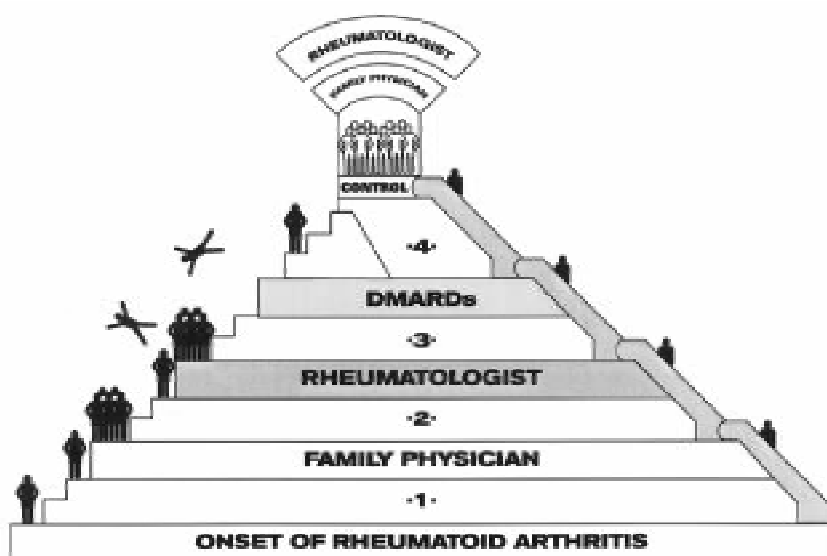


Fig. 3. "Front of the line" (escalated) care is essential for the best outcome in rheumatoid arthritis patients.

gaining or restoring the state of one's health.

"Personal best" means not just pain relief but the best control possible. Currently, we believe there is a wide gap between what most patients achieve and what is achievable. The ladder of treatment seen in Figure 1 is their therapeutic potential. Achieving only part of this potential, while statistically meaningful, is clinically insufficient. The gap between what most patients achieve and what is achievable represents the unresolved therapeutic opportunity.

### Achieving "personal best" in clinical practice

"Personal best", while a lofty ideal, is difficult to quantify and achieve in clinical practice.

Traditional practice falls short - only some of the patients, some of the time achieve disease control. Doctors, nurses and patients are constantly seeking the elusive grail of how to evaluate and summarize improvement in RA. Unlike hypertension or diabetes, RA is too complex and variable to be summarized in a simple number with the treatment to be altered accordingly. This dilemma is compounded by the lack of a common language between doctors and patients - patients and their doctors are often out of sync.

During the past decade questionnaires for disease activity and quality of life have been standardized and validated. These questionnaires give us both a retrospective summary on what has happened and, to those who use them in the clinic, a view of what is happening. Universal adoption of standard questionnaires in all clinical encounters would improve patient care, but we believe that many patients and doctors need an additional or different tool to evaluate and communicate disease and treatment progress.

In Hamilton we use an additional tool called Snapshot™ (Fig. 4) which is a composite of the subjective patient global assessment (from poor to best) and the doctor's objective assessment of inflamed joints. Snapshot™ shows both the doctor and patient where they stand and becomes the common language towards personal best.

The benefits of Snapshot™ are: simplicity; alignment; and relativity and direction. Simplicity is essential for routine clinical use. Alignment between doctor and patient is usual. Malalignment with a positive slope suggests that a patient's perception of the disease is more severe than the objective findings. In our experience many of these patients have co-existent depression and fibromyalgia. A negative slope often indicates that the patient is in denial, simply coping but legitimately unaware of the extent of his or her disease and must be counselled towards a more realistic assessment and approach towards their disease management. Relativity and direction determine

where a patient stands and where a patient must go. We find that the visual image is often more compelling than words alone.

Snapshot™ is not a stand-alone tool but should be combined with both clinical data and standardized questionnaires. We find that when we do not use Snapshot™ we arrive at poorer clinical decisions and outcomes than when we do use it. Snapshot™ encourages hope, treatment change and compliance, and a trend towards continuous improvement and personal best. During the past two years in our clinic Snapshot™ has become the common language interface and has consistently changed our treatment perspec-

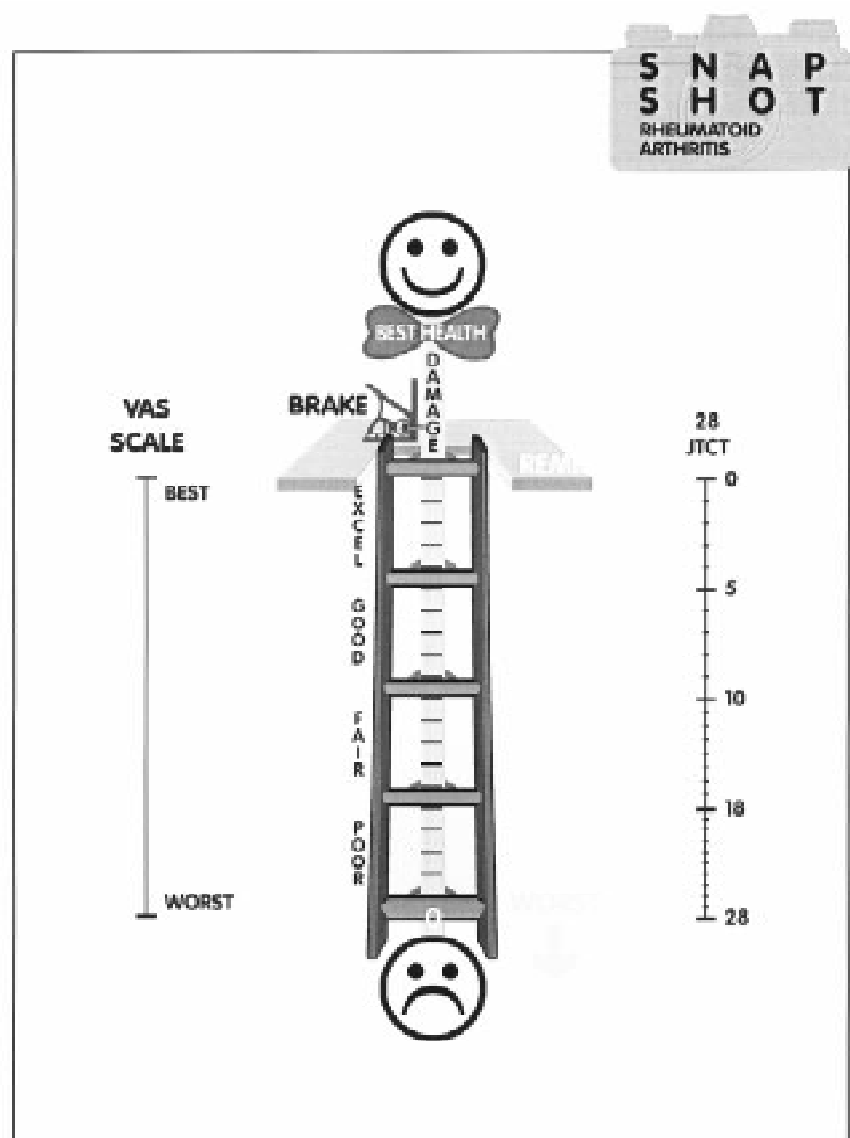


Fig. 4. Snapshot™, a clinical tool to evaluate "Personal Best" and physician/patient concordance.

tive. Further trials and evaluations to validate Snapshot™ will be necessary. Clearly personal best will not be universally achievable in clinical practice without a new paradigm of doctor/patient interaction and disease evaluation.

### Treatment principles of RA

Our approach to RA management is to treat the disease early, aggressively, selectively, and persistently (ASAP). The early, aggressive and persistent approaches are accepted by most rheumatologists, while the selective component remains controversial and will require confirmation through future trials and research. It is this selective component, however, that may be important in determining how and when combination DMARDs should be used.

Currently, the treatment options extend from the traditional "STEP UP" to combination DMARDs when monotherapy with DMARDs fails, to starting everyone on combination DMARDs followed by a "STEP DOWN" after disease control. Both approaches suggest that RA is a homogeneous disease requiring a relatively homogeneous treatment. Most clinical experience and some research suggest, however, that RA has a spectrum of inherent severities or "temperaments" ranging from mild to severe (5). These can be simplified for clinical usage as "mild, moderate, and severe." It is our view that this inherent temperament can be determined with relative accuracy even early in the course of disease by assessing a combination of: (i) the number and severity of joint involvement; (ii) the presence of extra-articular fractures; (iii) laboratory levels of the erythrocyte sedimentation rate (ESR), rheumatoid factor, and HLA typing; and (iv) high resolution ultrasound to determine synovitis and early erosions.

Rather than suggest the same treatment for all, we believe in selective treatment levels for different disease severities. In moderate or severe temperament RA, patients should "STEP ON" to combination DMARDs immediately, and only in mild disease should the initial therapy be mono-DMARDs or antiinflammatory drugs alone (Fig. 2). "Step on" rather than "step up" and/or "step down" saves time and works effectively in a clinical

situation to control disease. A further decade of observations, however, will be required to show whether selective treatment or homogeneous treatment of RA is more successful.

### Combination DMARDs: The Canadian experience

Canadian rheumatologists, through our National RDU and research networks, have aggressively pursued better control of RA. During the past 10 years in Canada, the pendulum has swung from mono-DMARDs to the frequent use of combination DMARDs, both in the "step on" and "step up" formats. At McMaster University, two early pilot studies suggested that cyclosporin A might be useful in combination with both MTX and gold for RA patients who had failed monotherapy (6). Soon after, the HERA study (Hydroxychloroquine in Early RA trial) demonstrated the efficacy and safety of hydroxychloroquine (HCQ) in early RA (7). The HERA follow-up trial suggested a better long-term prognosis in patients treated with HCQ (8). Canadian rheumatologists embraced HCQ as a safe and effective DMARD and wondered if it would be a logical choice for combination with MTX.

The pairing of HCQ and MTX is therapeutically appealing because these drugs are effective individually and possess complementary pharmacologic profiles.

HCQ alone is considered the least toxic of the widely used DMARDs and offers a better toxicity profile than 9 of 10 common nonsteroidal antiinflammatory drugs (NSAIDs) (9). Retinopathy is rare with HCQ at dosages of 6.5 mg/kg/day, so that initial and periodic ophthalmologic exams suffice to simplify the monitoring of this antimalarial (10). Whereas HCQ is initially slower to act, MTX compensates in combination with a rapid onset of action, making MTX a preferred DMARD selection despite the inherently more stringent monitoring it requires.

The combination of MTX plus HCQ has been studied further in two pilot trials published to date only in abstract form. The first trial was a prospective 16-week pilot study of 20 RA patients with a disease duration of less than two years who were treated with "step on" combination therapy with HCQ, MTX and intramuscular (i.m.) methylprednisolone (11). The results (Fig. 5) demonstrated a dramatic improvement in all parameters within 16 weeks except for the ESR, which was surprising to the investigators. HLA sub-typing, performed retrospectively to address concerns that these RA patients may have had mild, relatively non-progressive RA, revealed that 10 patients had no copy of the DR shared epitope for RA (consistent with milder disease), 8 patients had one copy (con-

### Efficacy Outcome Measures: Effect Sizes

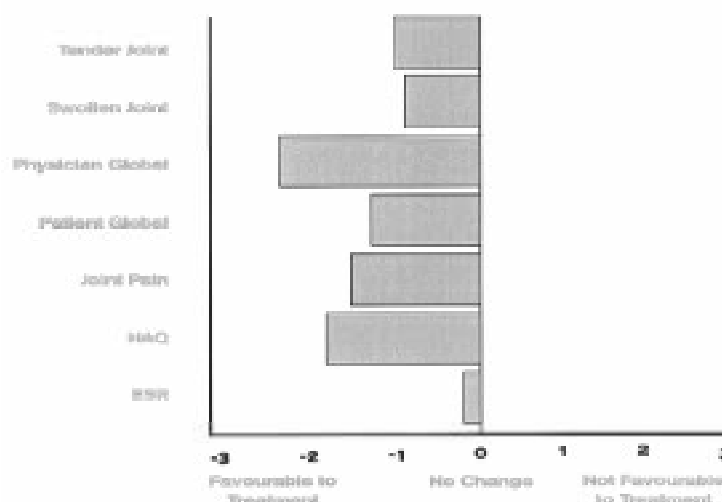


Fig. 5. Efficacy outcome measures in the Canadian "Step On Approach in Early RA" trial.

**Table I.** Efficacy outcome measures.

	Week 0 (mean $\pm$ SD)	Week 16 (mean $\pm$ SD)	Change $\pm$ SD 95% [C.I.]	P value
Tender joint count (0 - 68)	20.7 $\pm$ 12.8 (n = 20)	6.5 $\pm$ 7.6 (n = 20)	-14.3 $\pm$ 3.2 [-20.97, -7.53]	< 0.001
Swollen joint count (0 - 66)	14.7 $\pm$ 10.1 (n = 20)	4.4 $\pm$ 4.7 (n = 20)	-10.3 $\pm$ 2.3 [-15.01, -5.6]	< 0.001
Physician's global evaluation (1 = very good to 5 = very poor)	3.7 $\pm$ 0.75 (n = 20)	1.9 $\pm$ 0.79 (n = 20)	-1.8 $\pm$ 0.25 [-2.27, -1.23]	< 0.001
Patient's global evaluation (1 = very good to 5 = very poor)	3.6 $\pm$ 0.76 (n = 20)	2.1 $\pm$ 1.02 (n = 20)	-1.5 $\pm$ 0.27 [-2.0, -0.88]	< 0.001
Joint Pain	3.5 $\pm$ 0.83 (n = 20)	2.3 $\pm$ 0.73 (n = 20)	-1.2 $\pm$ 0.27 [-1.72, -0.58]	< 0.001
Pain - Visual analog scale (0 = none to 100 = very severe)	61.8 $\pm$ 23.5 (n = 20)	25.8 $\pm$ 23.5 (n = 20)	-35.9 $\pm$ 7.8 [-52.3, -19.6]	< 0.001
Health Assessment Questionnaire (HAQ)	1.7 $\pm$ 0.64 (n = 20)	0.5 $\pm$ 0.57 (n = 20)	-1.2 $\pm$ 0.18 [-1.54, -0.78]	< 0.001
Erythrocyte sedimentation rate (ESR) (Wintrobe)	40.9 $\pm$ 25.3 (n = 20)	35.4 $\pm$ 27.5 (n = 20)	-6.7 $\pm$ 6.4 [-20.0, 6.7]	0.306

sistent with moderate disease), and two patients were homozygous for the shared DR epitope (consistent with severe disease). The clinical features of these patients were related to their HLA subtypes.

The degree of therapeutic response was similar for all patients across the mild, moderate, and severe spectrum. This suggested that combination DMARDs play an important role in patients with moderate or severe temperment RA, for whom traditional therapy often fails to achieve significant clinical improvement. The clinical changes were dramatic. The mean tender joint count fell from 10.7 to 4.7 (68.8%) and the mean swollen joint count from 14.7 to 4.4 (70%). All patients stopped their steroid after the initial doses. The two patients with severe disease at 18 months were still in complete remission. In these two patients very early use of combination DMARDs may have fit into "a window of opportunity" to bring their disease under control (11). However, this was a single arm, non-placebo-controlled, observational study with all the inherent weaknesses of this type of study.

In the second study, 103 patients (age 18 to 80 years) who received HCQ in addition to their existing MTX therapy in

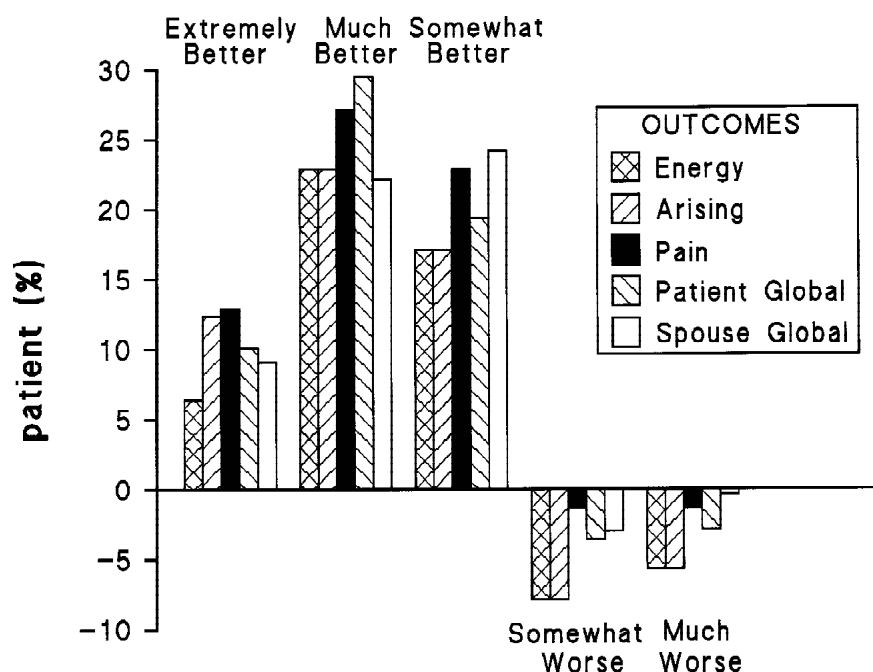
1995 were reviewed by a nurse clinician from October to December 1996. A chart review was completed on these patients and data were collected including the symptom onset time since diagnosis, RF, ESR, joint count, morning stiffness, disease activity, and functional status. Each patient also completed five questionnaires. A modified questionnaire was used to quantify their degree of pain, disease activity, and overall health using a 7-point Likert scale (1 = extremely better and 7 = extremely worse). The second questionnaire reported the d-HAQ variables as being either easier, the same, or harder. Spouses also completed a global assessment (Table I, Fig. 6).

Patients' perceptions of changes that they had experienced in the disease since starting combination therapy are shown in Figure 6. Most patients felt that their pain, morning stiffness, swelling, energy level, and activity level were somewhat better to much better after starting DMARD therapy. The majority of patients reported a large improvement in their overall health. A spousal questionnaire reported slightly less but also substantial improvement in the patients' overall health. Patients were asked to think about d-HAQ activities in terms of their being easier or harder to accomplish

since they had started their combination therapy. The majority of patients found these activities easier to accomplish since starting combination therapy (Fig. 6). These patients had longstanding disease with an average duration of 13 years. They had been satisfied with their current condition. Most had to be persuaded to initiate combination DMARD therapy because they did not believe that further improvement in their disease was possible. The degree of improvement both clinically and statistically surprised both the patients and the doctors and suggested that our clinic had a significant unresolved "Pincus Phenomenon." This study was a retrospective review of the patients' perception of change and had all of the weaknesses inherent with this approach (patient recall, etc). Another limitation was the absence of a control group of patients who were continued on monotherapy alone.

#### Literature review: HCQ + MTX

International support for administering HCQ plus MTX to early RA patients with moderate to severe disease arises from studies which suggest that this DMARD combination offers greater efficacy and opportunities for disease control, with fewer adverse reactions and a



**Fig. 6.** Changes in outcomes since the initiation of combination disease-modifying antirheumatic drug (DMARD) therapy. The chart summarizes the distribution of patient numbers across the Likert scale response categories describing the amount of change after the initiation of therapy.

possible additional benefit compared with monotherapy.

Trnavsky *et al.* reported excellent results in a 6-month, randomized, placebo-controlled study in which 20 RA patients treated with HCQ (200 mg/day) plus placebo improved in only 3 of 6 clinical variables and zero laboratory parameters, while 20 patients treated with HCQ (200 mg/day) plus MTX (7.5 mg/week) tolerated the therapy well and improved in all clinical variables. These variables included the articular index, the number of swollen/effused joints, minutes of morning stiffness, and pain on movement, with significant improvement ( $P = 0.05$ ) in both pain at rest and the Dixon's index. Significantly reduced ESR and circulating immune complex values were unique to the combination group, as was a reduced degree of radiologic disease progression that encourages further examination. (13).

A recent two-part study by Clegg *et al.* (14) confirmed not only that HCQ plus MTX significantly improved both the clinical and laboratory parameters for RA at 6 months, but also that subsequent maintenance with HCQ actually delayed the occurrence of flare ( $P = 0.023$ ). The first segment of this multicentre study was open label and involved treating 141

patients for 24 weeks with HCQ (200 mg bid) plus MTX (7.5 mg/week for 6 weeks, followed by up to 15 mg/week). MTX was then withdrawn, and responders ( $n = 121$ ) continued through a second double-blind, parallel segment of 36 weeks randomly assigned to 1 of 3 groups: (i) HCQ plus MTX as needed for disease flare ( $n = 40$ ); (ii) HCQ 400 mg/day ( $n = 41$ ); or (iii) placebo as needed with MTX for disease flare ( $n = 40$ ). Combination therapy in the first segment of the Clegg *et al.* study was effective and well tolerated, resulting in decreased mean swollen joint scores within all groups ( $P < 0.001$  versus baseline), decreased painful and tender joint scores within all groups ( $P < 0.001$  versus baseline), and improved values for other disease variables except for the duration of morning stiffness, which did not significantly improve in the HCQ group. The only between-group differences in the first segment were that group (iii) candidates tended to have class II or III disease versus class I disease compared with group (ii) ( $P = 0.048$ ), and the difference between groups (iii) and (i) approached statistical significance ( $P = 0.08$ ).

In segment two, the combined flare-free curve for groups (i) and (ii) (who received the same medication until the first

flare) was better than for group (iii) ( $P = 0.023$ ) over the 36 weeks. The first 8 weeks of segment two, however, showed similar flare-free curves for all three groups, especially (i) and (iii). At the end of 36 weeks, among only the patients who had not flared up to week 8, overall flare-free rates were higher for groups (i) (65%) and (ii) (72%) versus group (iii) (27%;  $P < 0.05$ ). Clegg *et al.* thus found HCQ to extend the flare-free duration curve benefits initially accrued from combination therapy with HCQ plus MTX.

An unanticipated, although noteworthy, discovery from combining HCQ with MTX is that it also appears to stabilize hepatic enzymes at normal levels. This may allow patients with elevated enzymes who otherwise respond well to MTX alone to continue receiving therapy. In a review of anti-rheumatic drug therapies used to treat 2600 RA patients enrolled in the multicenter ARAMIS Post-Marketing Surveillance Program, Fries *et al.* (15) found that MTX monotherapy resulted in the highest values for serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT). HCQ alone, however, resulted in the lowest values. The combination of MTX and aspirin further resulted in the highest SGOT and SGPT values, whereas HCQ combined with either MTX or aspirin yielded the lowest values after adjusting for age, sex, and the duration of disease.

A study was carried out in 1998 by Dr. Maria Suarez-Almazor (16) on the prescribing patterns of 25 Canadian rheumatologists choosing to modify DMARD monotherapy in 246 inadequate responders with RA. Dr. Suarez-Almazor found that, at the time of modification, most patients were already receiving MTX alone (39%) or HCQ alone (31%). The most common combination prescribed to the MTX-alone group was HCQ plus MTX (73%). Similarly, patients receiving HCQ were most often prescribed HCQ plus MTX (72%). This represents a definitive shift away from a decade of automatically switching non-responders over to alternative single DMARDs. For obvious reasons, there is a strong leaning toward combination therapy internationally and HCQ plus MTX in particular.

## Summary

During the past decade in Canada, RA has become a disease of hope rather than of despair due largely to the widespread institution of combination DMARDs. MTX combined with HCQ is the most widely used Canadian combination. Two Canadian pilot trials, the Step On Approach in Early RA, and the Step Up Approach in Progressive (13 years RA), both observed efficacy with combination MTX plus HCQ. Two published studies (13, 14) also support increased efficacy with MTX plus HCQ.

To achieve our goal of remission or "personal best" for every patient, we need to modify our management approach and our therapy with combination DMARDs. All RA patients must be brought to the "front of the line" for treatment. Ideally, treatment in patients with moderate or severe temperament disease should start with "step on" combination DMARDs. Patients with progressive (i.e., long-standing) RA often have an unrealized therapeutic opportunity which can be met by "step up" combination DMARDs. This unrealized therapeutic opportunity must be identified at each patient-doctor encounter in our striving for the goal of "personal best." In our hands Snapshot™ (Fig. 5) inserted within our patient assessment sheet (Patient Portrait™) makes it simple and effective to identify where patients stand and where

they need to go in order to achieve their personal best. We believe that Snapshot™ used widely would improve the care of RA patients.

RA is the most treatable disability in the western world. There remains a widespread Pincus Phenomenon, however, i.e., the perception that subjective satisfaction equals objective control, in far too many RA clinics. Combination DMARDs judiciously applied with the ability to measure results should help us to improve the prognosis of this disease.

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