Disease Modifiers: Making the Right Therapeutic Choices for Our Patients

LARRY W. MORELAND

ABSTRACT. Patients with rheumatoid arthritis (RA) who suffer an inadequate response to disease modifying antirheumatic drugs and biologic therapies represent a large segment of the RA population, so treating these patients is a major issue for physicians. The 4 case studies discussed in this article were presented at an American College of Rheumatology 2006 Annual Meeting Satellite Symposium and highlight some of the key issues for patients who are not responding adequately to current therapies. These issues include which therapy to consider next for maintaining tight control and maximizing outcomes in patients, and what is the rightful place of newly approved therapies within the current RA treatment armamentarium. Included here are the Audience Response System (ARS) results from the symposium, which will allow readers to compare their answers with that of the audience; this may help physicians in the decision-making process for their patients. (J Rheumatol 2007;34 Suppl 79:21-26)

Key Indexing Terms:
DISEASE MODIFIERS RHEUMATOID ARTHRITIS DECISION-MAKING THERAPY

INTRODUCTION

Patients with rheumatoid arthritis (RA) whose response to disease modifying antirheumatic drugs (DMARD) and biologic therapies is inadequate represent a large proportion of the RA population. Treating such patients is therefore a major challenge for physicians. In this article the 4 case studies discussed highlight some of the key issues for patients who are not responding adequately to current therapies.

Case 1

The first patient is a 72-year-old woman diagnosed with RA at 71 years of age. She was previously treated with nonsteroidal antiinflammatory drugs (NSAID) and hydroxychloroquine. When she presented to her physician, she had significant diffuse joint pain, swelling, and fatigue. Physical examination and laboratory findings showed a swollen joint count (SJC) of 14, a tender joint count (TJC) of 15, and high rheumatoid factor (RF) and anti-cyclic citrullinated peptide levels. Radiographs of her hands, wrists, and feet showed juxtaarticular osteoporosis and multiple erosions of the metacarpophalangeal joints (MCP), ulnar styloids, proximal interphalangeal joints (PIP), and metatarsophalangeal joints (MTP).

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Oral methotrexate (MTX) was initiated and titrated to 15 mg/wk, but at 3 months, she had minimal response. MTX was increased to 25 mg/wk parenterally. Six months into this treatment course, she still had minimal clinical response and active disease. Laboratory tests were carried out to determine whether switching therapy was needed. Hepatitis C serology and tuberculin skin tests were negative. She had a normal chest radiograph. She was up to date on all immunizations. Etanercept twice weekly was added to MTX 25 mg/wk.

After 6 months of etanercept/MTX therapy, she had mild synovitis across the PIP, MCP, and MTP joints and wrists bilaterally, SJC of 10, TJC of 11, and unchanged stiffness and fatigue. Radiographs revealed new erosions since she was initially diagnosed and prescribed MTX. Table 1 lists her laboratory values.

Table 1. Laboratory measures for Case 1.

Measure	Value
Hemoglobin	10.3 g/dl
White blood cell count	$5200 \times 10^3/\mu l$
Platelets	$420{,}000/mm^3$
ESR	44 mm/h
CRP	1.1 mg/dl (normal 0-1.0 mg/dl)
RF	125 IU (normal < 20 IU)
ANA	Negative
Albumin	3.0 g/dl

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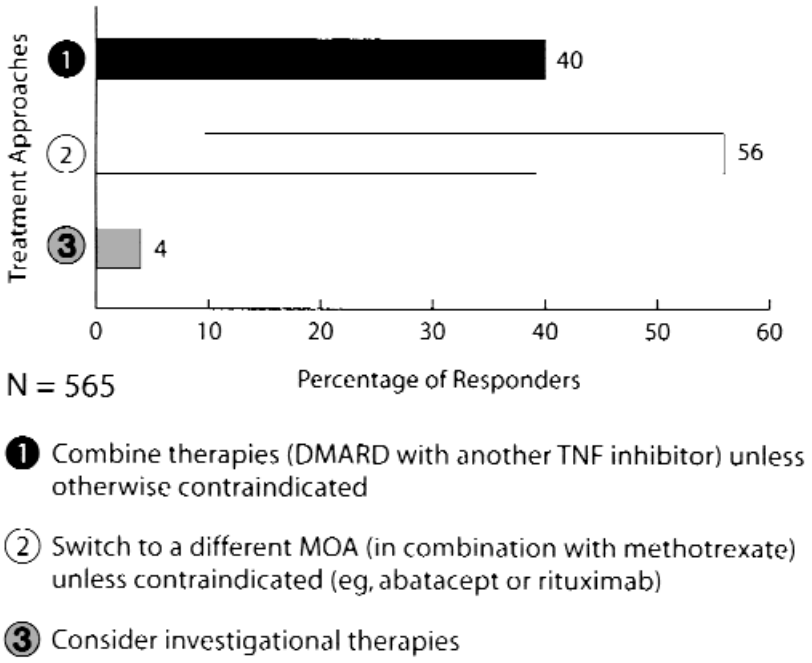

Figure 1. Audience response: Case 1. Based on this patient's disease activity, what treatment approach would you employ? MOA: mechanism of action.

Figure 1 shows the audience response to the following question: Based on this patient's disease activity, what treatment approach would you employ?

An interesting question arises whether this patient should be switched to another tumor necrosis factor (TNF) inhibitor or to a biologic with a different mechanism of action, such as abatacept or rituximab. As shown by the response in Figure 1, the audience was divided about the approach to take, but more than half would switch to one of the newer agents with novel mechanisms of action. There are no large, prospective, randomized studies on the safety or efficacy of switching from one TNF inhibitor to another. Only several small, uncontrolled switching studies have been carried out, and they demonstrated mixed results[1]. The consensus is that all TNF inhibitors are equally efficacious, but some patients respond to one and not another[2].

Both abatacept and rituximab have been studied in patients who are inadequate responders to DMARD and TNF inhibitors, and both are safe to use in combination with MTX[3,4]. In contrast to this, safety studies have shown that abatacept should not be used in combination with a TNF inhibitor as this leads to a higher incidence of infection[5]. No studies have addressed the coadministration of rituximab and a TNF inhibitor, but it has been shown that failure of rituximab does not preclude the use of another TNF inhibitor[6]. With the recent approval of abatacept and rituximab, there are still some unanswered questions about the order of TNF inhibitor use after a TNF failure. There are no data to suggest the order of use for rituximab and abatacept.

This patient was switched to a different TNF inhibitor, adalimumab 40 mg every other week, and then reevaluated at 3 months. Her symptoms persisted. Increasing the adalimumab to weekly administration also did not improve her clinical signs and symptoms. At this point, the physician should consider using alternative treatments, such as abatacept and rituximab.

Case 2

The second patient is a 60-year-old woman with a 6-year history of RA. She had no clinical improvement with MTX up to 17.5 mg/wk and was switched 3 months ago to sulfasalazine 500 mg bid, hydroxychloroquine 200 mg bid, and prednisone 5 mg/day. She presented with pain, poor functional status, and inability to make a fist. Table 2 lists her laboratory values.

Table 2. Laboratory measures for Case 2.

Measure	Value
RF	Positive
Anti-CCP	Positive
Platelets	300,000/mm^3
Serum creatinine	0.9 mg/dl
Liver enzymes	19 U/l
Hemoglobin	11 g/dl

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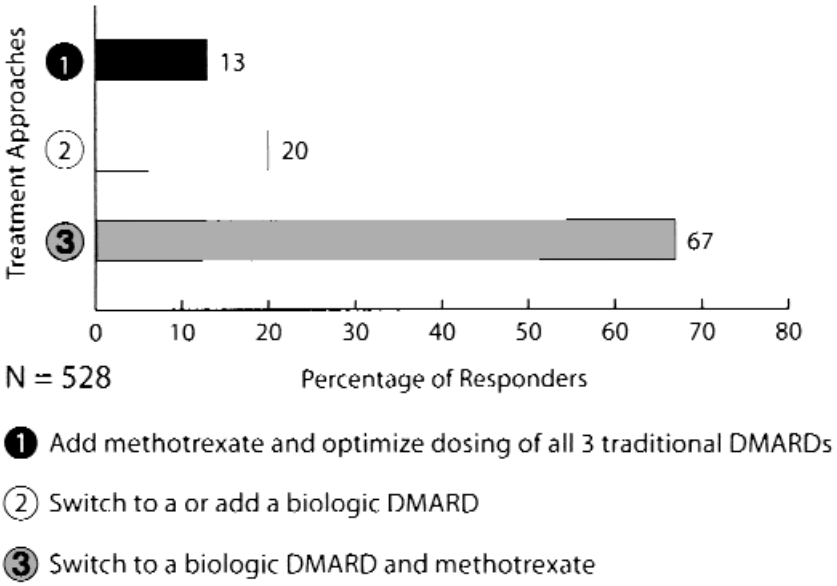

Figure 2. Audience response: Case 2. Based on your assessment, which management option would you choose?

Clinical evaluation showed a Health Assessment Questionnaire-Disability Index (HAQ-DI) score of 1.75 (on a scale of 0–3), a pain score of 7 (on a scale of 0–10), morning stiffness duration of 3 hours, SJC 14, TJC 16, and severe deformity of MCP and PIP bilaterally with subluxation, ulnar deviation, and moderate interosseous muscle atrophy. The clinical impression is that she has poorly controlled, severe RA.

Figure 2 shows the audience response to the following question: Based upon your assessment, which management option would you choose?

Conventional treatment with a single DMARD often fails to adequately control clinical symptoms or prevent disease progression. Longterm use of single DMARD has disappointing results[7], so traditional DMARD are most commonly used in combinations of 2 or 3 drugs[8,9]. Triple therapy with the combination of MTX, hydroxychloroquine, and sulfasalazine provides substantial benefit to many patients[10], but given this patient's clinical course, it would be prudent to switch to a biologic and reintroduce MTX. The Tight Control for RA (TICORA) study demonstrated the benefit of tight disease control in reducing disease activity and radiographic progression and in improving physical function and quality of life. Although tight control was achieved by standard DMARD in the TICORA study, their effect on radiographic progression was less remarkable than their effect on clinical disease indicators, and less impressive than results seen in clinical trials of TNF inhibitors[11]. A TNF inhibitor used in combination with MTX increases efficacy; this is a reasonable approach to manage poorly controlled severe RA.

Case 3

The third patient is a 45-year-old man with a 3-year history of RA. He has a 25-year history of smoking and frequent upper respiratory infections. He had pneumonia 8 months ago that required hospitalization and intravenous antibiotics. Most recently, his RA has been treated with leflunomide. He presented with bilateral soft-tissue swelling of the MCP joints, fusiform swelling of PIP joints, and SJC of 23. He is experiencing limitations in function and joint range of motion that interfere with his work as a carpenter. Morning stiffness lasts about 90 minutes. He claims that he has not had a recent cough or symptoms of an upper respiratory infection, and he is afebrile with a complete blood count within normal limits.

Figure 3 shows the audience response to the following question: Based upon your assessment, which management option would you choose?

The physician can be flexible when treating this patient. Options include switching to MTX monotherapy, adding MTX to leflunomide, switching to triple therapy with traditional DMARD, or switching to a biologic DMARD with or without MTX. Whichever strategy is selected, the goals are to minimize disease progression and alleviate symptoms.

Triple DMARD therapy has been shown to be more effective than MTX monotherapy or double DMARD therapy. Data from the German Biologics Register suggest that TNF inhibitors double the chance of remission compared to conventional DMARD therapies, although it should be noted that sustained remission occurred in a limited number of patients[12]. While the sustained remission rate with TNF inhibitors is not optimal, there are also data to support the

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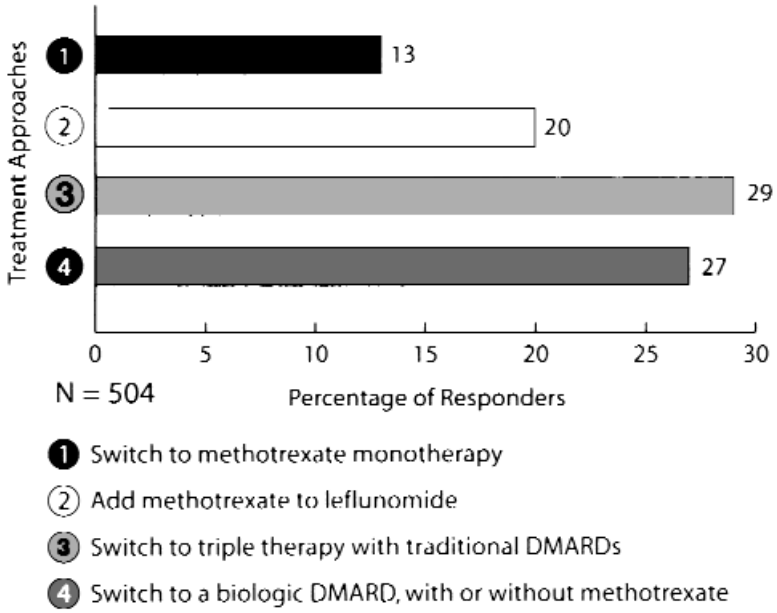

Figure 3. Audience response: Case 3. Based on your assessment, which management option would you choose?

use of TNF inhibitors for some patients with early RA. The PREMIER study demonstrated clinical remission in 43% and 49% of patients at Year 1 and Year 2, respectively, in patients who were treated with adalimumab and MTX early in the course of RA[13]. Similar results have been reported for infliximab and etanercept in patients with early RA[14,15].

Figure 4 shows the audience response to the following question: In this patient, are biologic DMARD contraindicated?

With this patient's history of infection, physicians may be hesitant to prescribe a TNF inhibitor for him. There are potentially some safety considerations with TNF inhibitors, including serious infections, opportunistic infections, and possible malignancies. Bongartz, et al published a meta-analysis in 2006 that examined a small number of patients, and suggests a 2-fold increased risk of infections and a 3-fold increased risk of malignancies in patients receiving TNF inhibitors[16]. These data are controversial and a number

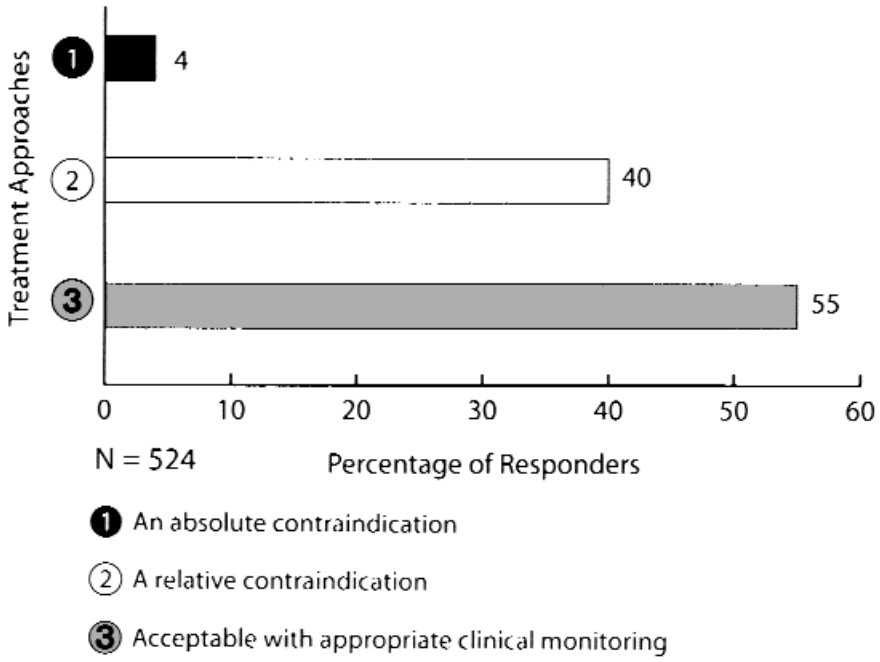

Figure 4. Audience response: Case 3. In this patient, are biologic DMARDS contraindicated?

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of recent reports have recommended caution when evaluating the results from this metaanalysis. One commentary was that the clinical trials were too small and the population studied was too selective, as the exclusion criteria affected the fairness of the control population and biased the infection and malignancy rates in favor of the treatment group, and the duration of the trial was too short to generate robust estimates for any increased risk[17]. In a followup study identifying the risk of serious infection using data from the British Society for Rheumatology Biologics Register, there was no increased risk of serious infection in patients treated with TNF inhibitors compared with that of the general population[18]. Physicians should be aware of the safety issues pertinent to TNF inhibitors that are still being addressed, and closely monitor patients receiving this class of therapy.

Case 4

The fourth patient is a 52-year-old man diagnosed with RA at 43 years of age. He presented to a new rheumatologist 6 months ago with SJC of 20, TJC of 16, and HAQ score of 1.6. He is currently treated with MTX 25 mg/wk and prednisone 10 mg/day. He has previously been treated with hydroxychloroquine, sulfasalazine, and leflunomide. His new rheumatologist prescribed etanercept twice weekly in addition to MTX 25 mg/wk. At his 6-month visit, he presented with more than 3 hours of morning stiffness, fatigue, malaise, a HAQ score of 1.2, SJC 10, and TJC 8. Table 3 lists his laboratory values at 6 months.

He was switched to infliximab 3 mg/kg but experienced no clinical improvement after 3 more months of treatment.

In the past, strategies to overcome inadequate response included escalating dose, increasing the dose frequency, switching within class (among DMARD or TNF inhibitors), switching to an interleukin 1 receptor antagonist, or combining therapies (multiple DMARD or DMARD plus TNF inhibitor). With the approval of abatacept and rituximab, which have unique mechanisms of action compared with the standard and biologic DMARD, switching to one of these newer therapies is a viable option. Both are approved for use after failure of at least one TNF inhibitor.

Table 3. Laboratory measures for Case 4.

Measure	Value
Hemoglobin	11.0 g/dl
White blood cell count	8200 × 10^3/μl
Platelets	580,000/mm^3
ESR	47 mm/h
CRP	1.3 mg/dl (normal 0-1.0 mg/dl)
RF	125 IU (normal < 20 IU)
Anti-CCP	Positive
ANA	Negative

For this patient, the infliximab dose was titrated from 3 mg/kg to 5 mg/kg administered every 6 weeks, but after 6 months, he still had minimal improvement in symptoms. He is a good candidate for switching to either abatacept or rituximab.

Conclusions

A number of treatment options are highlighted in these case studies. Each case addressed issues of how a physician could alter treatment if a patient suffers an inadequate response. While triple DMARD therapy is efficacious in comparison to monotherapy, with the advent of more effective biologics, patient outcomes can be optimized. TNF inhibitors are very effective, and rituximab and abatacept, which have been studied in patients who respond inadequately to DMARD and TNF inhibitors, expand the armamentarium of treatment options for patients with RA.

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