

# Improving Patient Outcomes: Emerging Data in the Treatment of Rheumatoid Arthritis

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# CME Information

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## TARGET LEARNERS

This activity is intended for rheumatologists.

## LEARNING OBJECTIVES

After completing this activity, participants should be able to:

- Interpret the impact on clinical decision making of new safety and efficacy data on emerging biologic therapies.
- Integrate early, aggressive treatment to prevent disease progression and joint damage.
- Integrate endpoints such as American College of Rheumatology (ACR) scores, Disease Activity Score (DAS), and radiographic remission into ongoing assessment of patients with RA.
- Assess and manage cardiovascular disease risk in patients with RA.

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# Remarks from the Chairperson

## **Leonard H. Calabrese, DO**

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The needs of our patients with rheumatoid arthritis (RA) are pressing. How best can we serve them? What are the prevalent views on treating patients early with agents that prevent radiographic progression? And is disease remission an achievable treatment goal? Data that address several of these questions also were presented, and these were discussed at the roundtable.

In 2009, our field of rheumatology is a garden of amazing therapeutic options. One thing that struck me after a decade, particularly a decade of using tumor necrosis factor (TNF) inhibitors, is that 2 more drugs in this class have been approved in the United States (certolizumab pegol and golimumab) to treat patients with RA. We have used the TNF antagonists in the clinic, and our patients have benefited tremendously from their use. In addition, a new option targeting the IL-6 pathway has been approved for use in the European Union (tocilizumab).

At this roundtable held at the European League Against Rheumatism (EULAR) 2009 meeting, we summarized the clinical development of these new agents, and discussed the long-term efficacy and safety data that were presented with respect to treating patients with RA. We also discussed their role, and the current goal of treating patients with RA. My colleagues who joined me at the roundtable have been involved at specific stages in the clinical development of these agents. They are, therefore, most knowledgeable about their efficacy and safety.

In addition, the EULAR 2009 meeting provided a discussion on the cardiovascular risks that patients with RA experience, and which are not explained by conventional cardiovascular risk factors such as hypertension and dyslipidemia. In treating RA, we are rightly focused on treating its signs and symptoms, but often fail to remember that we also need to look at the patient as a whole being. We must be aware of other extra-articular or systemic manifestations that these patients may be experiencing. As practicing rheumatologists, we need to be aware of these and address them appropriately.

This monograph is divided into 3 sections:

1. The first section discusses the advantages of early, aggressive treatment of patients, and why this approach is warranted.
2. The second section discusses the efficacy and safety data for the new biologic agents. It also discusses select data for some of the already approved agents.
3. The last section discusses the prevalence of cardiovascular risk factors in patients with RA, and provides ways for them to be managed in clinical practice.

We hope our discussion of these questions provides you with important practical information as you continue treating your patients with RA.

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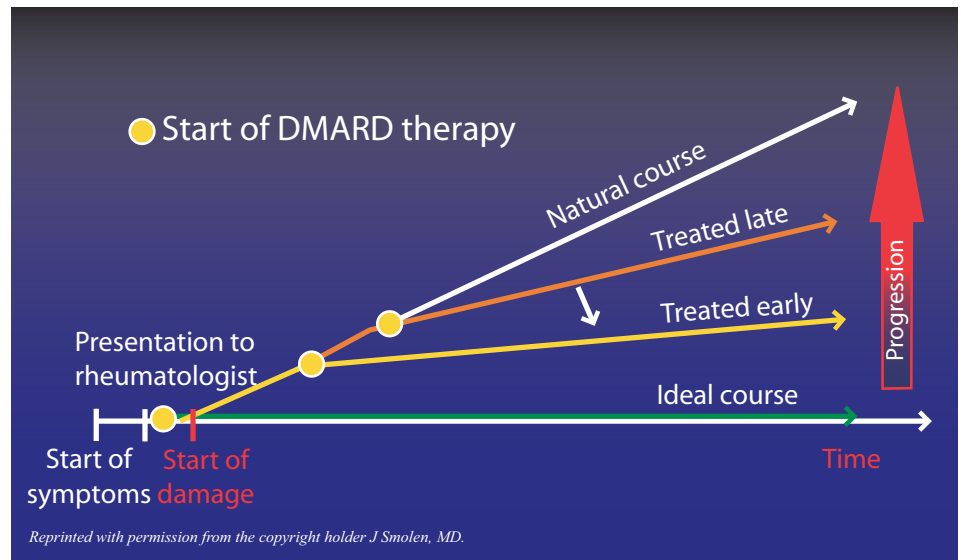
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# Early, Aggressive Therapy the Mainstay of Treatment

In the age of disease-modifying antirheumatic drugs (DMARDs), the goal of the rheumatologist treating RA was to decrease the signs and symptoms of RA. Using these biologics, these goals have been realized, and as new agents are added to the armamentarium of biologic DMARDs, rheumatologists are increasingly aware that their treatment paradigms must change for patients to acquire optimal benefits.<sup>1</sup> In patients newly diagnosed with RA, what should be the treatment goals? In patients with active disease, the question arises: What are rheumatologists treating? This particularly applies to patients who have markers of poor prognosis, who have high disease activity, and who have received the mainstay of therapy, methotrexate (MTX), in significant dosages.

The roundtable panel was unanimous that treat-to-target should be the mainstay of current treatment. The concept includes early, aggressive treatment of patients to a prespecified target that will prevent the progression of erosive disease and change the course of RA (Figure 1). However, the definition of early RA has been questioned. In a review on the importance of treating RA early, it has been acknowledged that most rheumatologists consider early RA as disease duration of fewer than 3 months. However, more than 50% of patients are often referred 6 months after signs and symptoms of RA. Several reports suggest that despite early treatment with a DMARD, joint damage may have already occurred.<sup>1,2</sup> With early,

**Figure 1: Altering the Course of Rheumatoid Arthritis**



aggressive treatment, patients have the possibility of better clinical outcomes. In fact, early, aggressive treatment provides a window of opportunity to change the course of RA compared with a more conservative approach.<sup>1</sup>

Most rheumatologists will agree that disease remission should be the outcome of treating to target. Although remission may be viewed as an absence of any significant inflammation, its definition is based on a measurement scale that is used in practice. Based on clinical practice, different scales have been used to define remission. Table 1 lists the scales that are used in clinical practice and in clinical trials. It also provides information that is needed to calculate disease remission for each.<sup>3,4</sup> For example, to calculate DAS28

remission, one would need to know the swollen and tender joint counts, the patient global assessment, and the level of an acute-phase reactant, which may be C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). A mathematical formula is then used to calculate DAS28.

All scales listed in Table 1, except the Routine Assessment of Patient Index Data (RAPID3) scale, take into account information based on swollen and tender joint count. The RAPID3 uses patient-based information on patient's global, physical, and pain functions to calculate remission.

The Disease Activity Scale is based on a 28-joint count of 2.6 (DAS28 <2.6) is one that is most commonly used in clinical studies. The Simplified Disease Activity

**Table 1: Disease Activity Measures for Rates of Remission<sup>3-5</sup>**

Definition of remission	SJC	TJC	Physician global	Patient global	Physical function	Patient pain	Acute -phase reactant (CRP or ESR)
DAS28 <2.6	√	√		√			√
SDAI ≤3.3	√	√	√	√			√
CDAI ≤2.8	√	√	√	√			
RAPID3 ≤1.0				√	√	√	
ACR	√	√		√	√	√	√

Abbreviations: ACR=American College of Rheumatology; CRP=C-reactive protein; CDAI=Clinical Disease Activity Index; DAS28=Disease Activity Score based on 28-joint count; ESR=erythrocyte sedimentation rate; RAPID=Routine Assessment of Patient Index Data; SDAI=Simplified Disease Activity Index; SJC=swollen joint count; TJC=tender joint count.

Index and Clinical Disease Activity Index are often used in compiling data from registry databases.

How do these scales compare with each other? The Consortium of Rheumatology Researchers of North America, Inc (CORRONA) registry determined that there was an overall fair to moderate agreement in remission rates based on the remission scales used in clinical practice.<sup>3</sup> While RAPID3 (a patient-based scale) requires the least amount of time, DAS28 remission is typically used in clinical studies.<sup>5</sup> In one report using random, patient-level data from clinical studies, it was determined that the choice of the composite index influences remission rates. In this report, while 30% of patients were in DAS28 remission, 8% and 7% of patients were in SDAI (Simplified Disease Activity Index) and CDAI (Clinical Disease Activity Index) remission, respectively.<sup>6</sup> The analysis concluded that acute-phase reactants can contribute considerably to clinical activity and disability but have little impact on SDAI and CDAI remission.<sup>6</sup> According to Dr. Emery, an important aspect of treat-to-target is that the target is predetermined. Physicians and patients predetermine treatment goals and the time within which they should be achieved. To this end, patients naïve to therapy should be monitored monthly, and then, more infrequently as the disease becomes stable. It is important to note that treat-to-target is not possible when patients have established disease and joint damage. The panelists also acknowledged that the philosophy of treat-to-target is independent of therapy and can be achieved with the use of DMARDs and/or biologic agents. With respect to DMARD therapy, common approaches used in treat-to-target are (1) continuous treatment with a combination of DMARDs, (2) a step-up approach that adds subsequent DMARDs when the target is not achieved with monotherapy, and (3) a step-down approach where treatment is initiated with a combination of DMARDs and, on achieving treatment target, one or more DMARDs contributing to significant toxicities is/are discontinued.<sup>1</sup> However, in any of these approaches using DMARDs, there is a greater likelihood of partial responses occurring more rapidly, which would require that treatment with biologic agents be initiated earlier to achieve a target. Using biologic therapy, treat-to-

**Table 2: Treat-to-Target Studies**

Studies	Conclusions
<b>BeST<sup>7</sup></b>	Tight control aimed at DAS28 <1.6 remission is more likely to be achieved in patients treated with initial combination therapy (initial combination therapy could be discontinued in approximately half the patients).
<b>CAMERA<sup>8</sup></b>	Computer-assisted model defined patients with early RA who received intensive treatment—the group that achieved better clinical remission (50% vs 37% for conventional strategy group) ( $P=0.03$ ).
<b>FIN-RACo<sup>9</sup></b>	Tight control defined as DAS28 <2.6 is achieved in more patients treated aggressively with a combination of DMARDs (at 11 years, ACR remission was achieved by 37% of patients taking combination DMARDs vs 19% for the individual DMARD group; $P=0.017$ ).
<b>TICORA<sup>10</sup></b>	Tight target (defined as DAS28 <1.6) was achieved with intensive management of RA compared with routine clinical care (65% of patients achieved disease remission in the intensive treatment group vs 10% for the routine treatment group) ( $P<0.0001$ ).
<b>COMET<sup>12</sup></b>	Treating early with etanercept prevents radiographic progression compared with treatment with methotrexate (50% of patients on combination etanercept and methotrexate achieved clinical remission vs 28% for patients taking methotrexate alone) ( $P<0.0001$ ).

*Abbreviations: ACR=American College of Rheumatology; BeST=Behandel Stratagieën; CAMERA=Computer-Assisted Management in Early Rheumatoid Arthritis; COMET=COmbination of Methotrexate and ETanercept in early rheumatoid arthritis trial; DAS28=Disease Activity Scale is based on a 28-joint count; DMARD=disease-modifying antirheumatic drugs; FIN-RACo=FINnish RA Combination Trial; RA=rheumatoid arthritis; TICORA=Tight COntrol for Rheumatoid Arthritis.*

target may be initiated with monotherapy to which one or more DMARDs may be added for better target control.

Several observational studies have examined how tight target control can be achieved in the framework of treating patients with RA (Table 2). In the BeST study (Behandel Stratagieën [Dutch for treatment strategies]), it was determined that the most beneficial approach is to treat patients aggressively using a combination of one or more DMARDs and either a biologic agent or prednisone to achieve tight target control. Medication is then tapered after tight disease control is achieved.<sup>7</sup> In the CAMERA (Computer Assisted Management in Early Rheumatoid Arthritis), FIN-RACo (FINnish RA Combination Trial), and TICORA (Tight COntrol for Rheumatoid Arthritis) studies, tight control or disease remission was achieved in significantly more patients with early RA who received intensive treatment compared with those who received routine clinical care.<sup>8-11</sup> The COMET study (COmbination of Methotrexate and ETanercept in early rheumatoid arthritis) included disease remission as the primary endpoint of the study, and has conclusively shown that it is achievable even in the setting of

clinical studies.<sup>12</sup>

These studies demonstrate that low disease activity or disease remission is possible when patients with early RA are treated aggressively to achieve tight target control. Although early aggressive treatment has been undertaken with combination DMARD therapy, the availability of biologic options suggests that DMARDs are more likely to be used early in RA treatment to achieve disease control, and perhaps, to reverse the course of disease. The need for aggressive treatment with biologic agents early in RA arises from observations that although patients may achieve remission with a DMARD, subclinical joint inflammation and deterioration can be detected using more sensitive imaging modalities, such as magnetic resonance imaging and ultrasonography—techniques that are not available for routine clinical use in the United States.<sup>13,14</sup> According to the roundtable panelists, practicing rheumatologists are not all convinced about the merits of treat-to-target, but given the mounting evidence in its favor, low disease activity or disease remission remains a goal that rheumatologists treating patients with RA should strive to achieve.

# Efficacy and Safety of Biologic Agents in the Treatment of Rheumatoid Arthritis

## THE NEW, APPROVED TNF ANTAGONISTS

Golimumab and certolizumab pegol are 2 new TNF antagonists that were recently approved by the FDA for treating patients with moderate to severe RA. The panelists summarized the clinical development of these agents.

### Golimumab

Golimumab is a humanized monoclonal antibody that binds to soluble and bioactive transmembrane forms of TNF. The efficacy and safety of golimumab has been evaluated in 3 inflammatory diseases: RA, psoriatic arthritis, and ankylosing spondylitis.

Pharmacokinetics studies showed that the half-life of golimumab is no different from that of any other TNF antagonists (approximately 2 weeks). Data from phase II studies indicated that golimumab 50 mg and 100 mg administered subcutaneously every 4 weeks is appropriate for evaluation in phase III clinical studies. Based on data from phase III studies, golimumab 50 mg sc, in combination with methotrexate (MTX), has been indicated for treating adults with moderate to severe RA.

The phase III, double-blind, placebo-controlled “GO” studies provided data on the efficacy and safety of golimumab in patients with RA. The GO-BEFORE (Golimumab Before Employing methotrexate as the First-line Option in the treatment of Rheumatoid arthritis of Early onset) study evaluated golimumab alone and in combination with MTX as first-line treatment in RA.<sup>15</sup> The primary endpoint of this study was not met; hence, golimumab was not deemed appropriate for the first-line treatment of

patients with RA. Data will be presented only for the approved dosing regimens of golimumab.

In the GO-FORWARD (Golimumab FOR subjects With Active RA Despite methotrexate) and GO-AFTER (Golimumab After Former anti-TNF Therapy Evaluated in RA) studies, the efficacy of golimumab was evaluated in patients with inadequate response to MTX and TNF antagonists, respectively. In both these studies, golimumab 50 mg sc in combination with MTX/DMARD provided significantly better responses compared with patients given MTX and placebo. However, responses achieved for golimumab monotherapy were not significant compared with those achieved with placebo + MTX/DMARD. In addition, in none of the studies were responses with golimumab 100 mg in combination with MTX significantly better than those achieved with golimumab 50 mg in combination with MTX.<sup>16-19</sup> Based on these data, golimumab 50 mg, in combination with MTX, was approved for the treatment of patients with moderate to severe RA. Table 3 summarizes week 24 data from these studies for the approved 50 mg sc dosage.

According to Dr. Emery, the efficacy of golimumab in treating ankylosing spondylitis and psoriatic arthritis is more impressive than that seen in treating patients with RA. The baseline disease burden seen in patients enrolled may explain this observation.

In RA current clinical trials, patients likely have lower disease activity compared with patients who enrolled in trials that evaluated the first-generation TNF antagonists (etanercept, infliximab, and

adalimumab). In the prebiologic era, patients with active disease were more readily available and, therefore, responses observed with the first-generation TNF antagonists were more impressive.

At the EULAR 2009 meeting, data from the GO-AFTER study were analyzed based on the number and type of prior TNF antagonist therapies that patients may have received. At week 14, ACR20 response rates were similar for patients who had received 1 or 2 prior anti-TNF agents (39% and 38% for 1 or 2 prior anti-TNF agents) and were significantly higher than patients receiving a DMARD.<sup>20</sup> The ACR and DAS28 responses indicated that similar responses were seen in patients who had previously received etanercept, adalimumab, or infliximab.<sup>20</sup> It was shown that effective ACR20 and ACR50 responses were seen in patients receiving golimumab, irrespective of whether they had previously received 1 or 2 TNF antagonists. Another report showed that baseline levels of CRP, a marker of inflammation and disease activity, were not a determining factor in responses achieved with golimumab.<sup>21</sup> All patients receiving golimumab showed higher ACR responses, although these were not always significant when compared with patients receiving placebo.<sup>21</sup> An intravenous formulation of golimumab administered every 3 months also was evaluated in the GO-LIVE study. Data at 48 weeks showed that patients who may not have responded at week 24 show responses at week 48.<sup>22</sup> According to Dr. Emery, although the intravenous formulation shows a clear efficacy when administered every 3 months, it does not show the robust response typically associated with TNF antagonists. Safety data from these

**Table 3: Efficacy of Golimumab in Combination With MTX at Week 24**

Efficacy endpoints	GO-FORWARD <sup>16</sup>		GO-AFTER <sup>18,19</sup>	
	Golimumab 50mg + MTX (n=89)	Placebo + MTX (n=133)	Golimumab 50mg + DMARD (n=153)	Placebo + DMARD (n=133)
ACR20	59.6%*	27.8%	34.0%*	16.8%
ACR50	37.1%*	13.5%	18.3%*	5.2%
ACR70	20.2%*	5.3%	12%	3%

\*P<0.001 vs placebo + MTX.

Abbreviations: ACR=American College of Rheumatology; DMARD=disease-modifying antirheumatic drug; GO-AFTER=Golimumab After Former anti-TNF Therapy Evaluated in RA; GO-FORWARD=Golimumab FOR subjects With Active RA Despite methotrexate; MTX=methotrexate.

short studies showed that golimumab has a safety profile similar to that of other TNF antagonists. Currently, there are no data for safety benefits with the 4-week dosing.

## Certolizumab Pegol

Certolizumab pegol is a pegylated form of the Fab fragment (the antigen-binding fragment) of a humanized anti-TNF- $\alpha$  antibody. It was developed for ease of manufacture, to have low immunogenicity, and to avoid complement activation. Its unique properties involve low injection site reaction, reduced activity in vitro for mast cells, and the potential not to cross the placenta. Although pegylation is expected to prolong the half-life of the agent, certolizumab pegol has a half-life similar to that of other anti-TNF antibodies (14 days) and has been approved for treating patients with moderate to severe RA based on data from the RAPIDI (Rheumatoid Arthritis Prevention of Structural Damage) and FAST4WARD (Efficacy and Safety of certolizumab pegol - 4 Weekly dosing in Rheumatoid arthritis) studies—both double-blind, placebo-controlled studies. Again, data will be provided for the approved dosing regimen for certolizumab pegol.

In the 52-week RAPID study, patients in the certolizumab arm of the study first received loading doses of 400 mg sc at weeks 0 and 2. Following loading doses, patients were administered certolizumab pegol 200 mg sc every 4 weeks. In addition, all patients received stable doses of MTX.<sup>23</sup> In the 24-week FAST4WARD study, patients in the certolizumab pegol arm were administered 400 mg sc every 4 weeks as monotherapy.<sup>24</sup> Data for the RAPIDI and FAST4WARD studies are summarized in Table 4. According to the roundtable panelists, dose loading is unique for certolizumab pegol, which is administered at 400 mg initially at weeks 2 and 4, followed by 200 mg every 2 weeks. The higher loading dose of 400 mg permits quick suppression of active disease and inflammation, after which the dose can be decreased to the lower dose of 200 mg. The idea is similar to the treat-to-target concept of early, aggressive treatment to suppress disease activity, prevent joint damage, and perhaps, achieve quick disease remission.

Data at EULAR 2009 indicated that patients who achieved a response at week

**Table 4: Efficacy for Certolizumab Pegol**

Efficacy endpoints	RAPIDI (at week 52) <sup>23</sup>		FAST4WARD (at week 24) <sup>24</sup>	
	CZP 200 mg + MTX (n=393)	Placebo + MTX (n=199)	CZP 400 mg (n=111)	Placebo + DMARD (n=109)
ACR20	53.1%*	13.1%	45.5%*	9.3%
ACR50	38.0%*	7.6%	22.7%*	3.7%
ACR70	21.2%*	3.5%	5.5%†	0%

\*P < 0.001.

†P < 0.05.

Abbreviations: ACR=American College of Rheumatology; CZP=certolizumab pegol; MTX=methotrexate; RAPIDI=Rheumatoid Arthritis Prevention of Structural Damage; FAST4WARD=Efficacy and Safety of certolizumab pegol - 4 Weekly dosing in Rheumatoid arthritis.

6 showed better outcomes after 52 weeks of treatment. Of patients who achieved a DAS28 <1.5 at week 6 (n=167), 81%, 62%, and 39% achieved ACR20, ACR50, and ACR70 responses, respectively, at week 52. Similar ACR responses were seen in patients who achieved DAS28 <1.8 at week 6 (n=143).<sup>25</sup> Two-year data from the RAPIDI study also were reported. While RAPIDI was a 52-week study, patients were allowed to enroll in an open-label extension study. After 100 weeks of treatment, it was reported that responses seen at 52 weeks were sustained at 100 weeks. At week 100, ACR20, ACR50, and ACR70 responses for patients receiving certolizumab 200 mg + MTX were 68%, 55%, and 36%, respectively.<sup>26</sup> In another analysis, data were reported for patients who withdrew from the RAPIDI study for lack of efficacy. These patients were enrolled in an open-label study where they were given certolizumab 400 mg every 2 weeks in combination with stable MTX doses. This subset of patients showed benefits of therapy at the end of 52 weeks, as evidenced from improvements in ACR and disability index (measured by the Health Assessment Questionnaire).<sup>27</sup> These data suggest that patients who do not respond to study drug in a blinded study may still benefit from long-term therapy.

Safety data for certolizumab pegol are available from the 2-year and the FAST4WARD studies. In the 2-year report, after 100 weeks of treatments, serious infections were reported in 10.5% and 11% of patients who were in the 200-mg and 400-mg arms of the RAPIDI study. Tuberculosis was reported in 1.8% and 1.2% of patients who were in the 200-mg and 400-mg arms. Sixteen new malignancies were reported in patients administered certolizumab

pegol, of which 4 were nonmelanomas.<sup>26</sup> The safety profile for certolizumab is, therefore, similar to that of other TNF antagonists. In the FAST4WARD study, 9 patients developed anticertolizumab pegol antibodies, which decreased the ACR responses seen in the study.<sup>24</sup> However, injection site reaction rates were lower in patients in the certolizumab arm of the study (4.5% and 13.8% for placebo).<sup>24</sup>

## Why do we need new TNF antagonists?

In discussing the place of golimumab and certolizumab pegol in the armamentarium of TNF antagonists, the panelists agreed that the TNF antagonists provide physicians additional therapeutic options, which may be important when switching between biologic agents. The panelists also concurred that because it was available, patients may prefer the option of a less-frequent dosing regimen. In that regard, golimumab is dosed monthly. Although certolizumab pegol is dosed once monthly, the 2 loading doses are administered once every 2 weeks. The development of golimumab indicated that it was associated with greater stability compared to other monoclonal TNF antagonists such as adalimumab or infliximab. It may, therefore, find use in patients who develop human antihuman antibodies with infliximab or injection site reactions with other TNF antagonists. Certolizumab pegol is associated with a lower incidence of injection site reactions, which also may be of significance when choosing between agents. In addition, although the risk/benefit of monthly injections suggests additional safety with respect to infections, data analyzing safety show no significant differences with respect to other TNF antagonists.

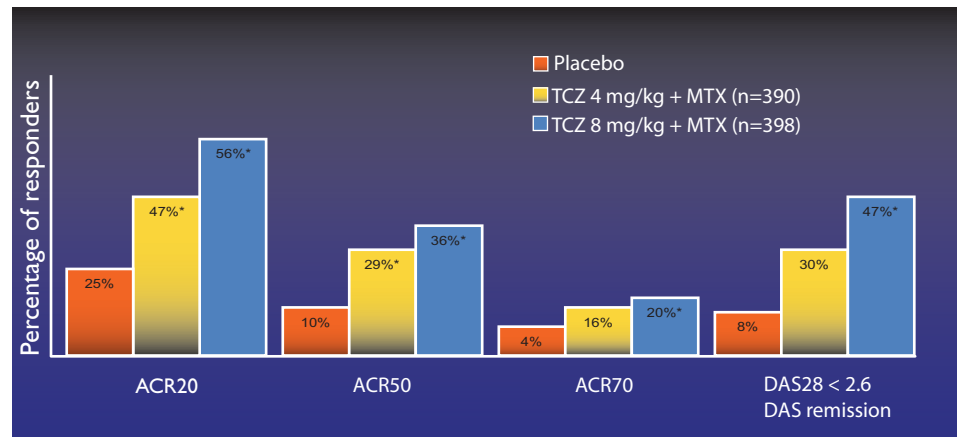
# TOCILIZUMAB—THE FIRST IL-6 RECEPTOR ANTAGONIST

Interleukin 6 (IL-6) is a pleiotropic cytokine with a wide range of biologic activities, which have implications in the pathophysiology of RA and other chronic inflammatory diseases.<sup>28-30</sup> It is found in elevated levels in the synovium and serum of patients with RA and has been associated with disease progression and joint damage.<sup>31-36</sup> In addition, elevated levels of IL-6 contribute to pannus formation and are involved in many of the systemic manifestations seen in patients with RA.<sup>37</sup> It seems appropriate that inhibiting the action of IL-6 may provide benefits to patients with RA and other inflammatory diseases.

## Efficacy for tocilizumab

Tocilizumab, the first IL-6 receptor antagonist, was developed by Professor Kishimoto in Japan where it was first approved for the treatment of patients with RA. Subsequently, it has been approved in the European Union, based

**Figure 2: ACR and DAS remission responses in patients with inadequate responses to DMARDs: The LITHE Study.<sup>39</sup>**



Abbreviations: ACR=American College of Rheumatology; DAS=Disease Activity Score; DMARDs=disease-modifying antirheumatic drugs; LITHE=tocilizumab safety and THE prevention of structural joint damage; MTX=methotrexate; TCZ=tocilizumab.

on its efficacy and safety in the largest phase III trial program for any biologic in RA. Five double-blind, placebo-controlled, phase III, randomized clinical studies have been conducted in patients with moderate to severe RA. These studies evaluated the efficacy of tocilizumab 8 mg/kg administered every 4 weeks. In some studies, tocilizumab 4 mg/

kg was also evaluated. The studies were not powered to compare the efficacy of the 8-mg/kg dose relative to the 4-mg/kg dose. Table 5 summarizes the data from 4 of these studies. Several points should be noted:

- In studies that evaluated the 4-mg/kg dose and the 8-mg/kg dose, tocilizumab 8 mg/kg always provided

**Table 5: Summary of Data From 4 Phase III Studies at Week 24**

Study	Treatment arms	Patient number	Response rates (%)			Remission rate (%) (DAS28<2.6)
			ACR20	ACR50	ACR70	
AMBITION <sup>38</sup>	TCZ 8 mg/kg	286	70*	44†	28‡	34
	MTX	284	53	34	15	12
OPTION <sup>40</sup>	TCZ 4 mg/kg + MTX	213	48*	31*	12*	13‡
	TCZ 8 mg/kg + MTX	205	59*	44*	22*	27*
	Placebo + MTX	204	26	11	2	1
TOWARD <sup>41</sup>	TCZ 8 mg/kg + DMARD	803	61*	38*	21*	30*
	Placebo + DMARD	413	25	9	3	3*
RADIATE <sup>42</sup>	TCZ 4 mg/kg + MTX	161	30§	17§	5	8
	TCZ 8 mg/kg + MTX	170	50§	29§	12¶	30¶
	Placebo + MTX	158	10	4	1	2

\*P<0.0001.

†P=0.0023.

‡P=0.0002.

§less than P<0.001.

¶less than P=0.001.

Abbreviations: ACR=American College of Rheumatology; AMBITION=Actemra versus Methotrexate double-Blind Investigative Trial in mONotherapy; DAS=Disease Activity Score; MTX=methotrexate; OPTION=tocilizumab Pivotal Trial in methotrexate Inadequate responders; RADIATE=Rheumatoid arthritis study In Anti-TNF failurEs; TCZ=tocilizumab; TOWARD=Tocilizumab in cOmbination With traditional dmARD therapy.

higher ACR and DAS28 remission responses compared with the 4 mg/kg dose.

2. The AMBITION (Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy) study enrolled patients who were predominantly MTX naïve.<sup>38</sup> In this study, tocilizumab monotherapy was shown to be superior to MTX with respect to ACR responses. In fact, tocilizumab monotherapy was reported to be superior to MTX as early as week 2 for ACR20 responses.<sup>38</sup> Although two-thirds of the patients were MTX naïve, ACR responses were also significantly higher than MTX when analyzed in MTX-naïve patients.<sup>38</sup>
3. Three studies established the efficacy of tocilizumab in patients with inadequate responses to DMARDs—LITHE (tocilizumab safety and THE prevention of structural joint damage),<sup>39</sup> OPTION (tocilizumab Pivotal Trial in methotrexate Inadequate respONDers),<sup>40</sup> TOWARD (Tocilizumab in cOmbination With traditional dmARD therapy).<sup>41</sup> After 24 weeks, DAS28 remission was seen in approximately one-third of the patients receiving tocilizumab 8 mg/kg.<sup>39-41</sup>
4. In the RADIATE (RheumAtoId arthritis study In Anti-Tnf failurEs) study, the efficacy of tocilizumab was

established in patients who had failed prior therapy with TNF antagonists either due to efficacy or safety.<sup>42</sup>

Thus, these studies established that tocilizumab can be used as monotherapy, and in patients with inadequate responses to DMARDs or TNF antagonists.

Data for the LITHE study were presented at EULAR 2009. Figure 2 summarizes data for the ACR and DAS28 responses. Figure 3 highlights data for suppression of radiographic damage.<sup>39</sup> Although DAS28 >2.6 remission was seen in approximately one-third of the patients administered tocilizumab 8 mg/kg, data from the LITHE study indicated that clinical benefits with tocilizumab continued to accrue over time. At 52 weeks, 47% of patients on tocilizumab 8 mg/kg were in DAS28 remission (Figure 2). The LITHE study also indicated significant suppression of joint damage as determined from the total Genant-modified Sharp scores, the joint erosion score, and the joint space narrowing score (Figure 3). The suppression of radiographic damage correlates well with changes in markers of inflammation and cartilage damage.

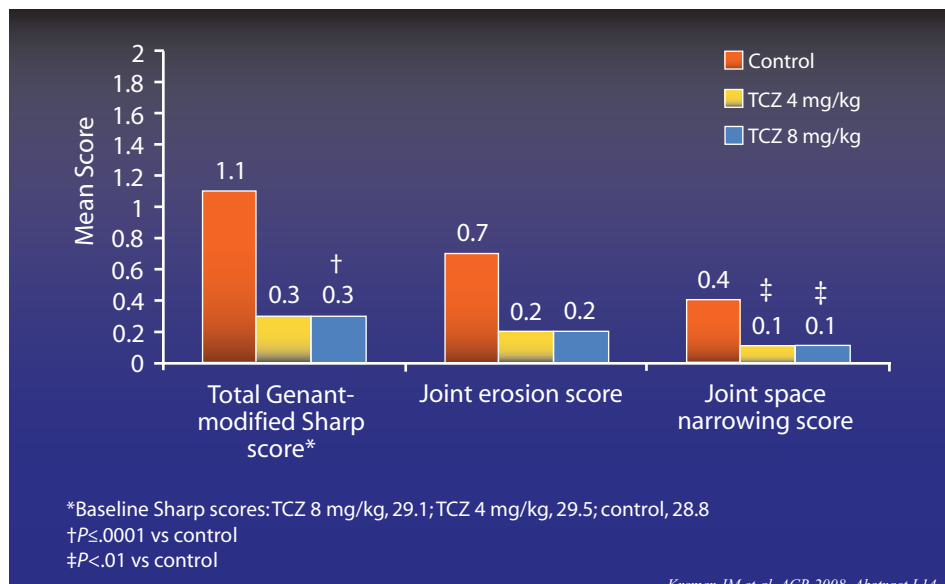
In the LITHE study, patients who achieved radiographic suppression with tocilizumab and MTX showed significant dosage-related changes in CRP and in markers of cartilage turnover such as type IIA collagen N-propeptide.<sup>43</sup> Other Japanese studies had earlier shown that tocilizumab suppresses radiographic

progression. However, the LITHE study was the only US registration study that evaluated the efficacy of tocilizumab in suppressing radiographic damage at 52 weeks.

Interim analyses of the long-term efficacy of tocilizumab also were presented at EULAR 2009. Patients from the 5 phase III studies (AMBITION, LITHE, OPTION, TOWARD, and RADIATE) had the option of enrolling in the long-term extension studies in which all patients received tocilizumab 8 mg/kg every 4 weeks for 5 years. Interim analyses were presented for 2.5 years of tocilizumab therapy. All ACR20, ACR50, and ACR70 responses continued to improve over time. Similarly, DAS28 remission rates increased across all patient populations (Figure 4).<sup>44</sup> In addition, response was sustained as shown from clinically significant improvements in the ACR core components (Table 6)<sup>44</sup> In the long-term extension studies, only 3% of patients withdrew because of a lack of therapeutic efficacy.

In another report, data for MTX-naïve patients from the AMBITION study were analyzed for ACR and DAS28 remission responses. ACR20, ACR50, and ACR70 responses in MTX-naïve patients were similar to those observed for the intent-to-treat (ITT) population.<sup>45</sup> Similar data also were observed for DAS28 remission (in MTX-naïve patients, 34.1% for tocilizumab 8 mg/kg vs 13.3% for MTX; in the ITT population, 33.6% for tocilizumab 8 mg/kg vs 12.1% for MTX).<sup>45</sup>

**Figure 3: Change in radiographic scores from baseline to week 52 using the total Genant-modified Sharp score.<sup>39</sup>**



Abbreviations: LITHE=tocilizumab safety and THE prevention of structural joint damage TCZ=tocilizumab.

## Safety for tocilizumab

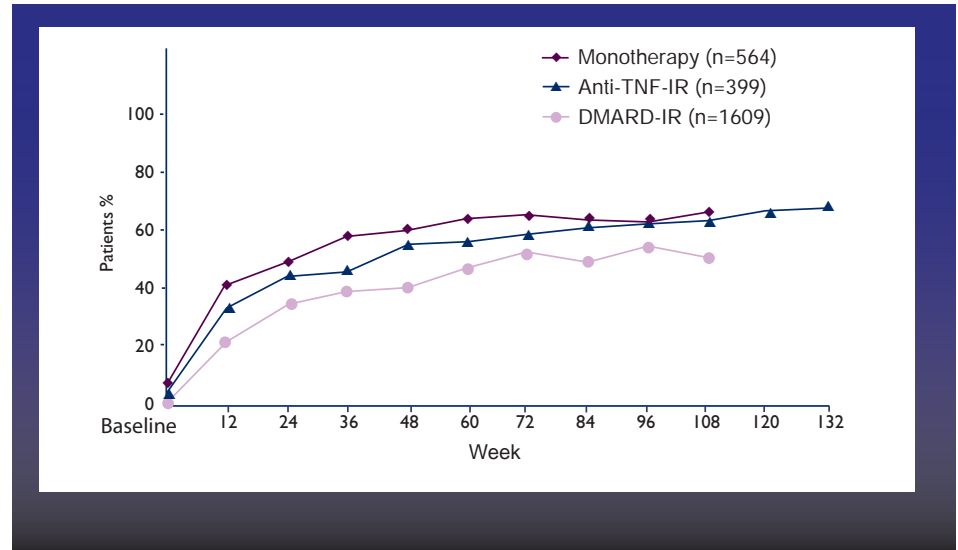
Detailed safety data at week 52 from the LITHE study showed that serious infections per 100-patient years occurred at a greater frequency in the tocilizumab group (4.0 for 8 mg/kg, 3.7 for 4 mg/kg, and 2.3 for MTX). Pneumonia was the most common infection and occurred at a similar frequency in all 3 groups. No events of tuberculosis were reported. Diverticular perforation occurred in one patient receiving tocilizumab 4 mg/kg. The patient had pre-existing diverticulitis and was withdrawn from the study.<sup>46</sup> Clinically significant anaphylactic reactions that required treatment discontinuation occurred in 6 patients receiving tocilizumab 4 mg/kg.<sup>46</sup>

The rates of malignancy per 100 patient-years were 0.86, 3.34, and 0.78 for patients in the tocilizumab 8 mg/kg,

4 mg/kg, and placebo + MTX groups, respectively. One lung neoplasm and one thyroid neoplasm observed in patients receiving tocilizumab 4 mg/kg were not confirmed as malignant.<sup>46</sup>

Neutropenia, lipid elevations, and elevated liver enzymes have been some of the lab abnormalities reported for patients receiving tocilizumab. In the LITHE study, grade 3 neutropenia was observed in 24 of 798 patients on tocilizumab. In 20 of these patients, it was seen at a single visit. In no patient was neutropenia associated with a serious infection. Three patients experienced grade 4 neutropenia and were withdrawn from the study. In these patients, neutropenia resolved within 4 weeks.<sup>46</sup> More patients receiving tocilizumab showed elevation in lipid levels (for low-density lipoprotein-cholesterol, 14%, 18%, and 4% for patients in the tocilizumab 4 mg/kg, 8 mg/kg, and MTX groups, respectively). Data also showed that these elevations were successfully managed with lipid-lowering agents.<sup>46</sup> Changes in ALT (alanine aminotransferase) to greater than 3 × ULN (upper limit of normal) were seen in 9%, 7%, and 0.8% of patients in the tocilizumab 8 mg/kg, 4 mg/kg, and MTX groups. Elevations in AST (aspartate aminotransferase) to greater than 3 × ULN were seen in 2.8%, 1.8%, and 0.3% of patients in the tocilizumab 8 mg/kg, 4 mg/kg, and MTX groups. Most of these were of single occurrences and normalized for patients without treatment or dosage adjustment. Drug-induced liver injury, including hepatic

**Figure 4: DAS28 remission through 2.5 years of therapy with tocilizumab.**



DMARD, disease-modifying anti-rheumatic drug, IR, inadequate response; TNF, tumour necrosis factor- $\alpha$ .  
 Note: n values shown are the total numbers of patients who reached the time points and had valid assessments.

dysfunction or clinical signs of hepatitis, was not reported. In addition, no patient showed concomitant elevations in liver enzymes AST/ALT > 3 × ULN) and total bilirubin (> 2 × ULN).<sup>46</sup>

Long-term safety in patients (n=3857) who received at least 1 dose of tocilizumab in the AMBITION, TOWARD, OPTION, and RADIATE studies was also reported after a mean treatment duration of 1.5 years. Cardiovascular events and malignancies did not increase with continued use of tocilizumab. In fact, rates were similar to those expected in the RA population. Rates of serious infections were stable over time (4.37 per 100 patient-years). Rates of upper and lower gastrointestinal

perforations per 1000 patient-years were 0.60 and 1.71. Grade 3/4 neutropenia was reported in 4% of patients, and no event was associated with serious infections. Elevations in AST and ALT > 3-5 × ULN were seen in 6.9% and 2.3% of patients. Again, these normalized and were not associated with clinically apparent hepatitis or drug-induced liver injury.<sup>47</sup>

In discussing the safety of tocilizumab, Dr. Choy noted that elevations in liver enzymes were seen when tocilizumab was used in combination with a DMARD, especially MTX. In fact, transaminase elevations were seen in fewer patients on tocilizumab monotherapy compared with MTX (the AMBITION study). The

**Table 6: Patients With Clinically Significant Improvements in ACR Core Components at Week 96<sup>44</sup>**

ACR core component	Tocilizumab monotherapy (%)	Anti-TNF IR patients (%)	DMARD IR patients (%)
0 TJC	21.2	15.5	25.7
0 SJC	36.1	22.5	34.9
0 TJC and SJC	16.8	8.9	19.0
≤1 TJC	32.7	21.1	36.8
≤1 SJC	49.1	29.6	46.0
Patient global VAS = 0 mm	13.2	3.0	4.5
Physician global VAS = 0 mm	10.8	2.4	8.4
Patient pain VAS = 0 mm	14.4	2.4	5.6
HAQ DI score = 0	24.6	8.9	17.1

Abbreviations: ACR=American College of Rheumatology; DMARD IR=inadequate response to disease-modifying antirheumatic drugs; HAQ DI=disease index as determined from Health Assessment Questionnaire; SJC=swollen joint counts; TJC=tender joint counts; TNF IR=inadequate response to TNF antagonists; VAS=Visual Analog Scale.

implication of these elevations was unclear. However, in clinical practice, persistent elevations to greater than 3 × ULN, especially with the combination of tocilizumab and MTX, would require 1 or both agents to be withdrawn to avoid the risk of clinically relevant hepatic toxicity. Dr. Choy indicated that transient liver enzyme increases do not pose an issue in clinical practice. Typically, patients administered tocilizumab are first evaluated for baseline laboratory values. After treatment, blood tests in patients are repeated to determine that elevations in laboratory values, when they occur, are transient. Liver elevations that are seen fairly early in treatment level off. Patients who are treated with tocilizumab in combination with MTX should be cautioned to avoid alcohol consumption.

According to the panelists, infections with tocilizumab were expected to be seasonal and bacterial in nature because IL-6 is important in B-cell responses and B-cell-related infections. IL-6 has not been implicated in animal models of tuberculosis and, therefore, its absence in clinical studies with tocilizumab was not surprising. The efficacy and safety of tocilizumab in all clinical studies, including the Japanese studies, has recently been the subject of an extensive review.<sup>48</sup>

## WHAT'S NEW WITH CURRENT BIOLOGICS

At the EULAR 2009 meeting, new data were presented for some of the existing biologics, including etanercept, adalimumab, and rituximab.

### Etanercept

Two-year data for the COMET study were presented by Dr. Emery. COMET was designed as a 2-year, randomized, placebo-controlled study that randomized patients in the first year to receive combination etanercept + MTX (EM) or MTX (M). The primary endpoint of the study was DAS28 remission. At the start of study, the combination EM arm was randomized to continue therapy with combination EM or to receive etanercept (E) monotherapy. Additionally, patients on the M arm were randomized to receive combination EM or continue receiving M. The randomizations for years 1 and 2 were all assigned when patients first enrolled in the study. At the end of the first year, DAS28 remission rates were 50% and 28% in patients receiving EM or M ( $P < 0.0001$ ).<sup>12</sup> The 2-year data summarized in Table 7 show that when patients who initially received EM were randomized to either EM or E, DAS28 rates continued to be high (57% vs 50% for EM and E, respectively). Notably, DAS28 remission significantly increased

in patients who initially received M and were switched to receive EM (58% vs 35% for EM and M) over the second year of therapy.<sup>49</sup> Radiographic nonprogression was highest when patients received the combination EM over the 2 years of the COMET study.

In their discussion, the panelists concurred with the conclusions of the COMET study—that treating patients early with first-line biologic therapy without increased toxicity provides the best clinical outcomes. The study actually provides evidence that if patients are first treated with MTX, although adding etanercept later provides the same level of disease activity, it does not do so without the cost of structural damage that occurred irreversibly in the first year. In addition, discontinuation of MTX from the combination is associated with loss of responsiveness to some degree. These data conclusively show the importance of initiating therapy with combination therapy.

The COMET study, however, does not answer the question whether it is possible to withdraw etanercept and retain remission with MTX after achieving initial remission with etanercept and MTX. The Remission induction by Remicade in RA study provides a clue that this is possible. In this report, based on an open-label study, 100 patients who achieved remission with infliximab and a DMARD were asked to discontinue infliximab. After 1 year, 27 patients had infliximab reinitiated because of symptom relapse. However, in 73 patients articular destruction did not progress despite discontinuation of infliximab.<sup>50</sup>

Data from other studies also support the importance of initiating combination therapy. In the CARDERA (Combination Anti-Rheumatic Drugs in Early Rheumatoid Arthritis) study, for example, the number of patients with new erosions was significantly reduced when treated early with the combination of MTX with either prednisolone or cyclosporin (16% vs 17% vs 29% for MTX/prednisolone, MTX/cyclosporin, and MTX) ( $P=0.03$  with prednisolone;  $P=0.01$  with cyclosporin). Benefits were greatest in patients who were treated with triple therapy consisting of MTX, prednisolone, and cyclosporin. The percentage of patients showing new erosions was the lowest (13%) in this group who showed the least amount

**Table 7: Two-Year Data From the COMET Study<sup>12,49</sup>**

Year 1 randomization	Etanercept + MTX (EM) (n=265)		MTX (M) (n=263)	
Remission at Year 1	50% (95% CI: 44%-56%)		28% (95% CI: 23%-33%)	
Year 2 randomization	EM→EM (n=111)	EM→E (n=111)	M→EM (n=90)	M→M (n=99)
Remission at Year 2	57%*	50%	58%*	35%
Δ mTSS	0.33	0.69	3.32	4.65
Patients with radiographic nonprogression	90%†	75%	75%	68%

\* $P < 0.01$  vs M→M.

†  $P < 0.01$  vs all other groups.

Abbreviations: mTSS=modified total Sharp scores; COMET=Combination of Methotrexate and Etanercept in early rheumatoid arthritis; CI=confidence interval.

of radiographic progression and had a better quality of life and improved disease activity.<sup>51</sup> Radiographic progression in the patients treated with MTX alone was much greater in 0-12 months compared with 12-24 months. Several reports at EULAR 2009 also showed that early, good response is predictive of better long-term clinical outcome.<sup>52-54</sup> In addition, even in patients with mild or moderate, persistent DAS28, step-up therapy with a DMARD continues to lead to functional deterioration.<sup>55</sup> These reports suggest that patients with combination therapy are more likely to achieve remission when treated early. In addition, as discussed previously, early intervention is essential and optimizes remission rates, especially when biologics are used in combination with a DMARD. With late disease (patients with RA who have failed therapy with a DMARD), remission cannot be sustained with cessation of biologic therapy. In one report, for example, delayed treatment with a TNF antagonist could only sustain remission in 15% of patients.<sup>56</sup>

However, is it ever possible to discontinue therapy after achieving disease remission? The BeST study examined the role of early treatment with DMARD and/or biologic agents in treating 508 patients with recent-onset active RA. Patients were targeted to 1 of 4 treatment strategies: group 1 received sequential monotherapy; group 2 received step-up DMARD combination therapy; group 3 received initial combination therapy with MTX, sulfasalazine, and prednisone; group 4 received an initial combination therapy with MTX and infliximab. Treatment was adjusted based on DAS (target DAS <2.4) calculated every 3 months. The study proved that more patients in groups 3 and 4 achieved DAS remission (DAS28 <1.6). In addition, more patients in group 4 could taper therapy and stop all treatment with antirheumatic drugs and sustain remission (17% vs 5% to 10% for other groups).<sup>7</sup> After 5 years, half the patients in the combination group were in low disease activity state without infliximab.<sup>57</sup>

## Abatacept

When launched 7 years ago, there was concern that treating patients with abatacept may disrupt cell-mediated immunity. Long-term efficacy and safety data for abatacept (available at EULAR 2009) indicated that long-term disease remission could be achieved

with abatacept. In the 7-year, long-term extension study, all patients from the double-blind, 1-year treatment study who enrolled in the long-term extension study received abatacept 10 mg/kg in combination with stable doses of MTX.<sup>58</sup> Of 219 patients who entered this phase of the study, 52% continued to receive treatment after 7 years. DAS28 remission and low disease activity improved over the 7-year study (DAS28 remission, 25.3% and 51.5% for years 1 and 7; low disease activity, 48.2% and 69.7% for years 1 and 7). Cumulative incidence of adverse events, serious adverse events, and serious infections per 100 patient-years were 366.1, 17.4, and 3.18, respectively. Malignancies were observed in 20 patients (24 events, 18 solid organ and 6 nonmelanoma skin cancers).<sup>58</sup> Autoimmune events, including psoriasis, were seen in 13 patients (4.5%). No case of tuberculosis was observed. These data provide evidence that long-term therapy with abatacept is safe and efficacious.<sup>58</sup>

In another long-term study of patients who were originally enrolled in the AIM (Abatacept in Inadequate responders to MTX) study, cumulative incidence of adverse events at the end of 5 years was similar to rates seen in the double-blind phase of the AIM study. Rates of infections and serious adverse events per

100 patient-years were 90.5 and 4.2 in the double-blind period and 67.1 and 2.8 in the cumulative, long-term extension phase. In this study, DAS28 remission also improved over 5 years and ACR responses were maintained.<sup>59</sup>

## Rituximab

Rituximab therapy is associated with depletion of a B-cell repertoire, an essential component of humoral immunity. Hence, there is concern about its use in clinical practice. With some long-term data available, the panelists felt that addressing issues pertaining to dosing with rituximab and its place in the treatment algorithm for patients with RA was appropriate for practicing rheumatologists.

The most significant presentation at EULAR 2009 was a study that evaluated the efficacy of rituximab in combination with MTX with respect to inhibiting radiographic progression and improving clinical outcomes for MTX-naïve patients with early, active RA.<sup>60</sup> Patients with no prior exposure to MTX were randomized to receive rituximab (2 × 500 mg) + MTX (n=239), rituximab (2 × 1000 mg) + MTX (n=244) or placebo + MTX (n=232). The 2 doses were given at fixed 6-month intervals. Table 8 summarizes the radiographic and clinical outcomes for the study. The primary endpoint of

**Table 8: Radiographic and Clinical Outcomes for Patients With Rituximab (RTX) and MTX at Week 52<sup>60</sup>**

	Placebo + MTX (n=232)	RTX (2 × 500 mg) + MTX (n=239)	RTX (2 × 1000 mg) + MTX (n=244)
<b>Radiographic outcomes</b>			
Mean change in mTSS	1.079	0.646	0.359 <sup>‡</sup>
Patients with change in mTSS	53.4%	57.7%	63.5%*
<b>Clinical outcomes</b>			
ACR20	64.3%	76.7%*	80.0% <sup>†</sup>
ACR50	41.8%	59.4% <sup>†</sup>	64.8% <sup>†</sup>
ACR70	24.9%	42.2% <sup>†</sup>	46.8% <sup>†</sup>
ACR90	9.2%	17.3%*	16.4%*
DAS remission	12.6%	25.4% <sup>†</sup>	30.5% <sup>†</sup>

\*P<0.05 vs placebo + MTX.

<sup>†</sup>P<0.0001 vs placebo + MTX.

<sup>‡</sup>P<0.001 vs placebo + MTX.

Abbreviations: ACR=American College of Rheumatology; DAS=Disease Activity Score; mTSS=Genant-modified Sharp scores; MTX=methotrexate; RTX=rituximab.

change in Genant-modified Sharp scores (mTSS) was met with the 1000-mg dose, but not with the 500-mg dose. The ACR responses were also significant after 2 doses with rituximab (Table 8). However, in his discussion, Dr. Emery focused on the fact that there was no radiographic progression in either treatment group after 6 months. Hence, the difference between the 2 treatment groups was accounted for within the first 6 months. This may help decrease the cost of biologic therapy, especially if patients can be dosed with rituximab 500 mg every 6 months.

Based on data from a study presented at EULAR 2009, Dr. Emery provided a management strategy for patients who did not respond to rituximab. In the study, 235 patients received the licensed dose of rituximab (2 IV doses of 1000 mg given 1 week apart). Of these, 30 patients (19%) did not respond to therapy. Ninety-two percent of nonresponders were shown to have persistent circulating B-lineage cells after the first infusion of rituximab (vs 48% for responders;  $P < 0.001$ ). In nonresponder patients, synovial B cells were more numerous. After retreatment with rituximab, B-cell numbers significantly declined. According to Dr. Emery, the suggestion that nonresponders have B-cell-independent disease is paradoxical. The reason patients do not respond in the first cycle is that

circulating B cells are significantly high in number. In fact, baseline B-cell levels are predictors of whether patients will respond to therapy with rituximab after the first cycle.<sup>61</sup> The report suggested that “retreatment of nonresponders with a second cycle of RTX [rituximab] before circulating preplasma cells return to baseline levels enhances B-cell depletion and results in better clinical responses.”<sup>61</sup>

In clinical practice, Dr. Emery suggested that patients should be retreated if symptoms flare or if a slight deterioration in signs and symptoms is observed. In cases where symptoms return after 6 months, patients should get a rapid reinfusion of rituximab. Given that response lasts for approximately 11.5 months, there is no rational basis to double the frequency of treatment. Further, data on multiple cycles are limited to 5 or 6 cycles. Hence, there was no logical basis for treating more patients with rituximab with greater frequency. Reduction in gamma globulins was also related to the number of courses (cycles) administered. Because treatment with rituximab eliminates an important component of an integrated immune response, caution is required for long-term therapy with rituximab compared with shorter-acting agents such as TNF antagonists. Long-term safety data in patients who were retreated with 5 cycles of rituximab indicate that rates of infection were similar to those seen in earlier cycles (Table 9).<sup>62</sup>

According to the panelists, the effect of B-cell depletion on immunoglobulins remained an issue. It was speculated that more than 25% of patients will have a decrease in their IgM isotype below the lower limit of normal (LLN). Five to 7% of patients will have their IgG isotype below the LLN. Although statistically not significant, there is a palpable increase in serious infectious episodes among patients who have IgG below the LLN. According to one report, patients with serious infections following treatment with rituximab may subsequently be treated with shorter-acting agents, such as TNF antagonists without an increased risk for infections.<sup>61</sup>

The panelists also discussed the occurrence of progressive multifocal leukoencephalopathy in patients receiving biologic therapy. Although this adverse event is currently not reported in the RA literature, recent sporadic reports of progressive multifocal leukoencephalopathy with rituximab in the transplant and oncology arenas have raised general concern in physicians using biologic agents. Severe and irreversible occurrence of progressive multifocal leukoencephalopathy may pose serious concern in patients with RA. Rheumatologists treating RA are advised to understand the risk factors for developing this devastating condition so that it does not become a prevalent complication of an effective therapy to treat RA.

**Table 9: Adverse Events (AE) by Course (C) of Rituximab Treatment per 100 Patient-Years (PYs)<sup>62</sup>**

	<b>C1 (n=2579)</b>	<b>C2 (n=1926)</b>	<b>C3 (n=1228)</b>	<b>C4 (n=794)</b>	<b>C5 (n=282)</b>
<b>Total PYs</b>	2594	1877	900	409	119
<b>Any AE</b>	379	313	319	329	330
<b>Serious AE</b>	18.3	17.4	16.6	12.0	13.4
<b>Infections</b>	97	94	108	102	96
<b>Serious infections</b>	4.66	3.62	4.22	3.91	5.87

# Rheumatoid Arthritis and the Risk for Cardiovascular Disease

There is mounting evidence that patients with RA are at a higher risk for cardiovascular morbidity and mortality compared with age-matched and sex-matched subjects in the general population. Several epidemiologic studies have highlighted this risk and have concluded that cardiovascular risk is higher in patients with RA and is not accounted for by traditional risk factors such as dyslipidemia, hypertension, and obesity.<sup>63-66</sup> For example, patients with RA are at a 1.5 times higher risk for cardiovascular mortality compared with normal subjects.<sup>66</sup> In addition, underlying cardiovascular causes accounted for mortality in approximately 50% of patients with RA.<sup>67</sup>

These data were reported at the EULAR 2009 meeting. Data from a Swedish RA registry of 7653 patients with newly diagnosed RA were matched for age, sex, marital status, and residential area (n=37 837). Within the first decade of diagnosis of RA, risk of myocardial infarction (MI) in these patients was 1.7 (95% CI: 1.3-2.3).<sup>68</sup>

The data emphasize the need to identify patients with RA with increased risk of cardiovascular morbidity and mortality in clinical practice. Data suggests that the extent of inflammation might provide clues to identifying these patients. Even in normal subjects, for example, elevated levels of inflammatory cytokines (eg, TNF- $\alpha$  and IL-6) and elevated levels of acute-phase proteins (eg, CRP and serum amyloid A) have been associated with cardiovascular risk.<sup>69,70</sup> It is not surprising that in patients with RA, inflammation itself has been identified as an important risk factor for cardiovascular disease and mortality in patients with RA.<sup>71</sup> According to one report, when compared with a non-RA cohort, the 10-year absolute cardiovascular risk in the RA populations increased in the presence of traditional risk factors (from 16.8% to 60.4% such as smoking, hypertension, dyslipidemia, diabetes, and obesity).<sup>72</sup> The increased risk may be associated with elevated levels of inflammatory cytokines influencing endothelial dysfunction in patients with RA.<sup>73</sup>

How does inflammation contribute to cardiovascular risk? It has been proposed that synovitis in patients with RA can lead

to accelerated atherogenesis. Elevated levels of inflammatory cytokines such as TNF- $\alpha$  and IL-6, for example, leave inflammatory sites and are released into the general circulation. These circulating inflammatory molecules are in a position to alter the function of distal tissues such as adipose, skeletal muscle, liver, and the vascular endothelium, where proatherogenic changes occur, leading to endothelial dysfunction and accelerated atherogenesis.<sup>74</sup>

Thus, it may be possible to use disease activity in RA to identify patients at high risk for cardiovascular morbidity and mortality. In a presentation at EULAR 2009, functional disability and DAS28 could predict high-risk patients. For example, a patient with a 1-point increase above DAS28  $\geq 3.1$  was predicted to have a relative risk increase of 1.41 for cardiovascular disease.<sup>75</sup> In another presentation, baseline disease duration, elevated levels of hs-CRP, and functional disability (as identified from HAQ scores that predicted cardiovascular disease) defined the occurrence of hypertension, angina, cardiac disease, stroke, or myocardial infarction).<sup>76</sup>

These studies provide clues to identify RA patients with high risk for cardiovascular disease. Currently, neither the ACR nor EULAR have recommendations on how cardiovascular risk should be identified and managed. With overwhelming evidence that increased cardiovascular morbidity and mortality are seen in patients with RA, a EULAR task force was established to determine how cardiovascular risk may be managed in clinical practice. At the EULAR 2009 meeting, an evidence-based approach provided the basis of a consensus statement on how patients with RA and other inflammatory diseases should be monitored and managed for cardiovascular risk.<sup>77</sup> The following steps form the basis of a consensus statement to be published on how patients with RA should be managed in clinical practice<sup>77</sup>:

- a) Recognize that RA is associated with increased cardiovascular risk.
- b) Adequately control RA disease activity, which also decreases cardiovascular risk.

- c) Use local and national guidelines on an annual basis to assess cardiovascular risk before and after initiating treatment for RA.
- d) Apply risk score models to RA patients; add an additional weighting of 1.5 if 2 of the following 3 criteria are met: rheumatoid factor positivity or anticyclic citrullinated peptide antibody positivity, RA longer than 10 years, or presence of certain extra-articular manifestations.
- e) When cardiovascular risk is identified, intervene with lipid-lowering agents and/or hypertensive medications according to national guidelines, statins, ACE inhibitors, and/or angiotensin II receptor blockers.
- f) The use of cyclo-oxygenase inhibitors, nonsteroidal anti-inflammatory drugs, and steroids were not recommended; if used, they were recommended at the lowest possible dosages.

The panelists also provided guidance on how cardiovascular risk in patients with RA is managed in their own practice. In one practice, the electronic medical record has automatic pop-ups that ask if patients with RA, vasculitis, or lupus have been referred to a preventive cardiology clinic, where they would be treated to accelerated endpoints. In another practice, lipid levels are determined before starting treatment for RA. In cases of high lipid profiles, advice is sought from cardiologists for best management strategies. Following treatment for RA, lipid levels are re-evaluated.

Elevations in lipid levels, especially in the context of treatment with tocilizumab, were discussed. Clinical studies on tocilizumab have identified elevated lipid levels in a significant proportion of patients. Dr. Choy suggested that treatment with tocilizumab may unmask underlying high lipid levels in these patients. As discussed in a review, increased inflammation or high CRP levels seen in inflammation have a significant effect on lipid levels in patients. Inflammation actually suppresses lipid levels, and hence, patients who may normally have elevated lipid levels have lower levels in the context of RA.<sup>78</sup> Because tocilizumab inhibits the IL-

6-mediated signaling, the acute-phase response is rapidly suppressed. CRP levels rapidly decrease, and these correspond to elevations in lipid levels.<sup>78</sup> However, although long-term studies are warranted,

in all tocilizumab studies, elevations in lipid levels were not associated with cardiovascular events.<sup>78</sup> Similar increases have incidentally also been reported with

the use of TNF antagonists.<sup>78</sup> In clinical practice, elevated lipid levels have been successfully managed with lipid-lowering agents.

## Conclusion

### CONCLUDING REMARKS FROM DR. CALABRESE

This discussion is meant to help rheumatologists in their practice. We understand that many of our colleagues may be cautious in treating their patients with RA. We hope that the data discussed will help in changing the treatment paradigm.

There should be no doubt that treating to target endpoints must be the primacy of all treatments. Because it helps prevent radiographic progression, remission is

desired for all our patients. Data indicate that this is realized by treating our patients with a combination of biologic agents and DMARDs. Patients achieving remission early are likely to retain the response, and over time, it may even be possible to discontinue treatment until the disease flares. We also provided insights into the 2 new TNF agents that have been added to our armamentarium of TNF antagonists. Besides, we have summarized the clinical trials for tocilizumab, the first IL-6 receptor antagonist that has been approved for treating patients with moderate to severe RA in Europe and

that awaits approval in the United States. The long-term use of tocilizumab will resolve some of the questions that have arisen in clinical trials—neutropenia, and elevations in lipid and liver enzyme levels. Finally, cardiovascular risk in patients with RA can no longer be ignored in our clinical practice. The EULAR Task Force consensus statement that will soon be published should provide guidance on how we manage our patients in clinical practice. We need to acknowledge the risk, identify patients at high risk based on the degree of disease activity, and treat any evidence of cardiovascular disease based on national guidelines.

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# Evaluation

## LEARNING OBJECTIVES

After completing this activity, learners should be able to:

- Interpret the impact of clinical decision making of new safety and efficacy data on emerging biologic therapies.
- Integrate early, aggressive treatment to prevent disease progression and joint damage.
- Integrate endpoints such as American College of Rheumatology (ACR) scores, Disease Activity Score (DAS), and radiographic remission into ongoing assessment of patients with RA.
- Assess and manage cardiovascular disease risk in patients with RA.

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## EVALUATION

Please rate this CME activity according to the scale below:

- 5 = Excellent  
4 = Very Good  
3 = Good  
2 = Fair  
1 = Poor

Extent to which learning objectives were met:

Interpret the impact of clinical decision making of new safety and efficacy data on emerging biologic therapies.

5     4     3     2     1

Integrate early, aggressive treatment to prevent disease progression and joint damage.

5     4     3     2     1

Integrate endpoints such as American College of Rheumatology (ACR) scores, Disease Activity Score (DAS), and radiographic remission into ongoing assessment of patients with RA.

5     4     3     2     1

Assess and manage cardiovascular disease risk in patients with RA.

5     4     3     2     1

Was this publication free of commercial bias?  Yes     No  
If no, please explain.

\_\_\_\_\_  
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What is the greatest challenge in your rheumatology practice?

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\_\_\_\_\_

What other topics would aid your knowledge and practice of rheumatology?

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# Post-test

To receive your CME credit, please complete the post-test below.

Credit will be issued by the Interstate Postgraduate Medical Association for participants who correctly answer at least 70% of these questions. Participants who do not achieve a passing score on the post-test will have the opportunity to retake the test one time. A CME certificate will be mailed within approximately 3 weeks of receipt of your completed registration, post-test, and evaluation.

Circle the appropriate response to each question or incomplete statement. Only one answer is correct.

1. Which of the following is true about the treat-to-target concept in treating patients with RA?
  - A. Patients should be treated with biologics after failure of DMARD therapy.
  - B. Patients should be treated early and aggressively to achieve disease remission.
  - C. Patients should achieve ACR20 responses within 6 months of treatment.
  - D. Patients should be treated cautiously with sequential DMARD therapy.
2. Which of the following is a patient-based instrument for measuring disease remission?
  - A. SDAI (Simplified Disease Activity Index).
  - B. CDAI (Clinical Disease Activity Index).
  - C. DAS28 (Disease Activity Score based on a 28-joint count).
  - D. RAPID3 (Routine Assessment of Patient Index Data).
3. Which of the following statements is true about the COMET study?
  - A. ACR20 response at Week 24 was the primary endpoint.
  - B. ACR50 response at Week 24 was the primary endpoint.
  - C. DAS28 remission was the primary endpoint.
  - D. ACR20 at Week 14 was the primary endpoint.
4. Which of the following clinical studies evaluated the efficacy of tocilizumab in preventing radiographic progression and achieving ACR responses as its primary endpoint?
  - A. The COMET study.
  - B. The LITHE study.
  - C. The RADIATE study.
  - D. The BeST study.
5. Which of the following is true about certolizumab pegol and golimumab?
  - A. They can both be dosed once monthly.
  - B. They both have a half-life of approximately 2 weeks.
  - C. They were both evaluated in patients with inadequate response to prior therapy with TNF antagonists.
  - D. They have both been approved for use in patients with failure to therapy with TNF antagonists.
6. Which of the following best applies to treating patients with RA with rituximab?
  - A. It is associated with T-cell depletion.
  - B. It is dosed once every other month.
  - C. Insufficient efficacy at the end of the first 6-month cycle may be indicative of incomplete B-cell depletion.
  - D. Its use even in other therapeutic areas is not associated with progressive multifocal leukoencephalopathy.
7. Patients who have achieved disease remission with early, aggressive treatment will always have to remain on therapy to maintain the remission they experience. Is this statement?
  - A. True?
  - B. False?
8. Which of the following statements is true about tocilizumab safety data?
  - A. Elevations in liver enzymes and total bilirubin were not seen concomitantly in patients.
  - B. Lipid elevations are always associated in patients with AST/ALT elevations.
  - C. Decrease in neutrophil counts was always associated with the occurrence of a serious illness.
  - D. Reactivation of tuberculosis occurred at a similar frequency as with other TNF antagonists.
9. Which of the following is a true statement about increased cardiovascular (CV) risk seen in patients with RA?
  - A. CV risk is due to traditional risk factors such as dyslipidemia and hypertension.
  - B. CV risk does not decrease following treatment for RA.
  - C. Inflammation is an additional risk factor.
  - D. CV risk is the same as that seen in the general population.
10. CV risk in patients with RA may be managed in which of the following ways?
  - A. Patients at high risk are identified and managed based on national guidelines.
  - B. Patients at high risk are identified and aggressively managed with high doses of COX2 inhibitors.
  - C. For patients with lipid elevations, a watch and wait approach should be used. Only after consistent elevations over 3 months, should patients be managed with lipid-lowering agents.
  - D. CV risk is automatically managed following treatment for RA.



