Clinical Perspectives from Around the Globe: Data Presented at EULAR 2008

Therapeutic Role of the IL-6 Receptor Antagonist Tocilizumab and TNF Blockers in Rheumatoid Arthritis

Editors

Leonard H. Calabrese, D.O.
Professor of Medicine
Cleveland Clinic Lerner College of Medicine
of Case Western Reserve University
RJ Fasenmyer Chair of Clinical Immunology,
Vice Chairman, Department of Rheumatic
and Immunologic Diseases

Eric Ruderman, M.D.
Associate Professor of Medicine,
Division of Rheumatology
Northwestern University Feinberg School of Medicine

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Therapeutic Role of the IL-6 Receptor Antagonist Tocilizumab and TNF Blockers in Rheumatoid Arthritis: Clinical Perspectives From Around the Globe: Data Presented at EULAR 2008

Contents

Course Description

The three available TNF blockers infliximab (Remicade®; a chimeric anti-TNF- monoclonal antibody), etanercept (Enbrel®; a recombinant soluble TNF receptor IgG_1-Fc fusion protein), and adalimumab (Humira®; a human anti-TNF-α monoclonal antibody) comprise the core of biological therapy for the treatment of RA. The efficacy and safety of TNF blockers, initially demonstrated in over 6000 patients enrolled in numerous clinical trials, has been reproduced in routine clinical practice.[1,2] Improvement in functional status and clinical signs and symptoms of disease, as well as inhibition of radiographic progression of disease, has been demonstrated following treatment with the TNF blockers.

Despite the advances achieved with the TNF blockers, the results of some clinical trials suggest that 30-50% of treated patients may fail to achieve an adequate level of improvement in response.[3] This clinical finding mirrors the evidence that RA pathogenesis is not restricted to a single cytokine. Rather, symptoms of RA result from a disruption in the balance of a proinflammatory-anti-inflammatory cytokine network that is not necessarily limited to a single cytokine pathway.[4]

IL-6 is a potent proinflammatory cytokine produced in increased amounts in RA.[5,6] Early studies revealed that IL-6 levels may correlate with RA disease severity. IL-6 is involved in every phase of RA, including recruitment of cells into the synovium, activation of fibroblast-like synoviocytes, and maturation of osteoclasts responsible for joint destruction. IL-6 also exerts systemic inflammatory events, namely, the production of C-reactive protein (CRP), and the anemia of chronic disease (through hepcidin production in the liver).[7-10]

Tocilizumab is a novel biological agent directed against both the soluble and cell-bound IL-6 receptor.[11] Results from several preliminary clinical trials have provided evidence of safety and efficacy in the treatment of RA, either as monotherapy or in combination with methotrexate (MTX).[12,13] Placement of tocilizumab in the treatment armamentarium for RA is currently under investigation.

The present ACCME-accredited Newsletter provides a concise, comprehensive summary of efficacy and safety associated with tocilizumab and TNF blocker therapy, as presented at the 2008 EULAR conference. Since the agents have not been studied head-to-head, clinical trial results will not be directly compared. Rather, the summary will provide clinical context to aid rheumatologists and allied healthcare workers in the rational use of TNF blockers and tocilizumab. The summary will address patient selection issues and shed light on the effects of the biologics on systemic manifestations of inflammation associated with RA.

Learning Objectives

When the target audience has completed the CE activity, they will be able to:

- Make a preliminary evidence-based judgment on the rational placement of tocilizumab and the TNF blockers for the biological treatment of RA, within the framework of the current RA treatment recommendations.
- Describe the efficacy and safety of tocilizumab demonstrated in pre-approval clinical trials conducted in early and later RA, and against methotrexate therapy.

Medicine Accreditation Statement

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Target Audience

This activity is designed to educate rheumatologists, infusion nurses, and pharmacists treating patients with rheumatoid arthritis.

Faculty

Eric Ruderman, MD, Associate Professor of Medicine
Division of Rheumatology
Northwestern University Feinberg School of Medicine
Chicago IL

Leonard Calabrese, DO, Professor of Medicine,
Cleveland Clinic Lerner College of Medicine
of Case Western Reserve University
RJ Fasenmyer, Chair of Clinical Immunology, Vice Chairman,
Department of Rheumatic and Immunologic Diseases
Cleveland OH

Development

This educational activity was developed by:

Carolynn E Pietrangeli, PhD, Senior Research Scientist
CTI Clinical Trial and Consulting Services
Cincinnati OH

Faculty Disclosure

It is the policy of the University of Kentucky to ensure balance, independence, objectivity and scientific rigor in all of its educational activities. In accordance with the policy of the University of Kentucky, faculty members are asked to disclose any affiliation or financial interest that may affect the content of this activity.

Dr. Calabrese has served on Speakers' Bureaus for Abbott, Amgen and Genentech and received consultation fees for Amgen, Biogen, Centocor, Elan, Genentech and Roche.

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Introduction

The EULAR conference held in Paris June 11-14, 2008 provided an update of treatment recommendations for rheumatoid arthritis (RA) based on experience with nonbiologic and biologic disease modifying anti-rheumatic drugs (DMARDs). Along with long term efficacy and safety results of the approved TNF blockers, current results of clinical trials with emerging biologics, including the IL-6 receptor (IL-6R) antagonist tocilizumab (TCZ) were discussed.

The present Newsletter is designed to summarize state-of-the-art results of established and emerging treatments for RA, as presented at EULAR. The Newsletter will discuss the EULAR presentations in the context of recommendations for the use of nonbiologic and biologic DMARDs published earlier in 2008.[14]

New Treatment Strategies in RA: Implications of the 2008 ACR Recommendations

Recent publication of American College of Rheumatology (ACR) recommendations for the use of nonbiologic and biologic DMARDs to treat RA provides an opportunity to review EULAR findings in the context of current clinical practice goals.[14] Based on a systematic review of scientific evidence, the ACR addressed the indications for use of nonbiologic and biologic DMARDs, assessment of the clinical response, and monitoring for side effects. For biologic DMARDs, recommendations were also made for the screening of tuberculosis and the role of cost and patient preference in treatment selection.

While the ACR recommendations clearly account for TNF blocker adverse events, they also reflect the efficacy profile of these drugs, reproduced in multiple clinical trials, as well as in clinical practice over the last decade. The recommendations reflect and set the trend for earlier use of TNF blockers in patients with established or potentially more serious disease.

The ACR recommendations are appropriately based on disease activity, as scored by several clinically relevant systems, and evidence of prognostic markers of disease progression **(Table 1)**.

Table 1. RA High and Moderate Disease Activity and Prognostic Markers of Disease Progression

	DAS28	SDAI	CDAI	RADAI	PAS or PASII	RAPID
High	>5.1	>26	>22	>4.9	>5.3	>12
Moderate	>3.2≤5.1	>11≤26	>10≤22	>2.2≤4.9	>1.9≤5.3	≥6≤12
Low	≤3.2	≤11	≤10	<2.2	<1.9	<6
Poor Prognostic Markers	Functional limitation, existence of extraarticular disease, RF+ and/or anti-CCP antibody+ disease, and/or evidence of bony erosions					

CCP: cyclic citrullinated peptide; CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score in 28 joints; PAS: Patient Activity Scale; RADAI: RA Disease Activity Index; RAPID: Routine Assessment Patient Index Data; RF: rheumatoid factor; SDAI: Simplified Disease Activity Index;

Recommendations for the Use of TNF Blockers to Treat Rheumatoid Arthritis

The ACR recommendations assert the primacy of methotrexate (MTX) and leflunomide as monotherapy for RA of all durations and severities. However, citing the evidence that TNF blockers improve disease activity and quality of life, and retard radiographic disease progression, the ACR has further recommended that TNF blockers be used in combination with MTX in patients with high disease activity of less than three months duration, in the presence of poor prognostic indicators.[14]

Specifically, ACR recommends the use of TNF blockers in early RA, defined as disease of less than 6 months diagnostic duration, in DMARD-naïve patients with high disease activity **(Table 2)**. The recommendation extends to patients with high disease activity of less than 3 months diagnostic duration who also have poor prognostic markers of disease progression. In these patients, ACR recommends the combination of a TNF blocker with MTX.

Table 2. Evidence-Based Recommendations for the Use of TNF Blockers to Treat RA[14]

Use of TNF blockers in early RA (<6 months)
- Patients with high disease activity who have never received DMARDs
- In combination with methotrexate, in patients with high disease activity for <3 months who have poor prognostic markers

Use of TNF blockers in intermediate-duration (6-24 months) and longer-duration (>24 months) RA
- Patients with prior inadequate response to methotrexate
  - With moderate disease activity and poor prognostic markers
  - With high disease activity, regardless of prognostic markers

The use of TNF blockers is also recommended in patients who have been diagnosed with RA for between 6 and 24 months and for longer than 24 months, with prior inadequate response to MTX. Poor prognostic markers should be present in candidate patients with moderate disease activity. In contrast, patients with high disease activity should be considered for therapy, regardless of the presence of poor prognostic indicators.

State-of-the-Art Results of TNF Blocker Therapy for Rheumatoid Arthritis

Underscoring the role of proinflammatory cytokines in disease pathogenesis, the introduction of TNF blockers has significantly changed the medical management of RA. No direct head-to-head clinical trials of infliximab, etanercept or adalimumab have been performed to date. However, the results of systematic reviews and meta-analyses suggest that the drugs demonstrate similar effectiveness with respect to clinical, radiologic, and health related quality of life indicators of disease.[15-17] Generally speaking, the adverse events profile of the three agents is similar, though a tendency to develop more severe adverse events, including severe infection, has been noted by some authors in patients receiving infliximab.[15]

The major clinical themes surrounding the use of TNF blockers, as presented at EULAR, are summarized in **Table 3**.

Table 3. Use of TNF Blockers — Major Clinical Themes Presented at EULAR

Long-term efficacy and safety
- Clinical and radiologic improvement, quality of life
- Risk of tuberculosis and malignancy
- Effects on liver enzymes and serum lipids

Treatment of early RA
- GUEPARD Trial
- NEO-RACO Trial
- COMET Trial

Treatment following failure of TNF blockers

Emerging TNF blockers
- Certolizumab and golimumab

Approved TNF Blockers

The results of studies presented at EULAR echo the ACR recommendations to use biologic therapy earlier in the RA disease process, to encourage clinical and radiologic response and to prevent joint erosion. A summary of the study results appears in **Table 4**. Management of patients who fail initial TNF blocker therapy is also of concern. Two studies presented at EULAR addressed this issue.

Table 4. TNF Blocker Therapy — State-of-the-Art Presentations at EULAR 2008

Theme	Patient Population	Treatment/Comparator	Results
Long-term Efficacy and Safety			
Efficacy/safety at 10 years of follow up[18]	N=2054/9763 pt-years European/N. American DMARD-refractory RA N. American — early RA (≤3 years) participating in open-label extensions of double-blind controlled trials	Etanercept Pts continuing therapy • 3 years: 57-71% • 9 years: 35-43%	ACR20/ACR50/ACR70: 70-76%/48-58%/31-37% Improved (Data not reported) • HAQ results • Swollen joint counts • CRP levels Deaths • Expected: 107 • Actual: 63

Table 4. (Cont.) TNF Blocker Therapy — State-of-the-Art Presentations at EULAR 2008

Theme	Patient Population	Treatment/Comparator	Results
Long-term Efficacy and Safety			
Risk of mortality at 8 years of follow up[19]	Swedish Biologics Register (ARTIS); N=67,150 n=6403 treated with TNF blockers 1998-2006	Patients treated with TNF blockers vs. those not receiving TNF blockers	SMR: RA pts receiving TNF blockers vs. general population=1.57 (1.42-1.73) RR mortality=0.85 (0.77-0.95) for RA pts. receiving TNF blockers vs. those not receiving
Incidence of malignancy[20]	Pts with RA 1998-2006 represented in Swedish Biologics Register (ARTIS); N=66,995 Cross-referenced with Swedish Cancer Register 1998-2005	EULAR DAS28 good, moderate or nonresponders to TNF blockers for treatment of RA	RR Cancer: • RA pts vs. general population=1.04 (0.89-1.21) • RA pts treated with TNF blocker vs. not treated with TNF blocker=0.94 (0.80-1.12) • No trend with respect to cumulative exposure to TNF blockers
Incidence of tuberculosis **RATIO Trial**[21]	Pts with • RA n=40 • Ankylosing spondylitis n=14 • Psoriatic arthritis n=3 • Crohn's disease n=7 • Takayashu's arteritis n=1 • Bechet's disease n=1	Case controlled study of pts treated with TNF blockers 2004-2006	Incidence of TB (per 100,000 pt-year): • General population (France) — 8.7 • Etanercept-treated — 6.0 • Infliximab- or adalimumab-treated — 71.5 Multivariate risk factors for development of TB: • Use of adalimumab vs. etanercept HR=10.05 (1.92-52.61); *P*=0.006 • Use of infliximab vs. etanercept HR=8.6(1.38-53.78); *P*=0.02 Median duration of TNF blocker therapy to development of TB: 52 weeks (range 6-321 weeks)
	RA pts treated with TNF blockers or DMARDs BSR Biologics Register	TNF blockers n=9882 Etanercept n=5265 Infliximab n=3569 Adalimumab n=3907 DMARDs n=2883	TB: 29/9882 • 55% TB cases extrapulmonary • Unadjusted IRR vs. DMARD: 4.7 (0.6-34.8) • Higher rates in pts treated with infliximab or adalimumab
Effects on liver enzymes **CORRONA Registry**[23]	N=6861 treated with TNF blockers 2001-2007	TNF blockers • Adalimumab n=849 • Etanercept n=1383 • Infliximab n=1449 TNF blockers + MTX New users of TNF blockers	Incidence of abnormal LFTs among pts receiving TNF blockers: Based on 22,522 LFT results • LFT >1xULN: 17.6% • LFT >2xULN: 2.1% Infliximab and adalimumab associated with elevated LFTs; no association with etanercept therapy
Treatment of Early RA			
COMET Trial[24]	Active, early RA (≤2 years) • 79% without prior DMARD use • 92% with severe disease (DAS28 >5.1)	**A:** Etanercept + MTX n=265 vs. **B:** MTX n=263	**52-week follow up** Remission: **A:** 50%; **B:** 28%; *P*<0.001 Radiographic non-progression: **A:** 80%; **B:** 59%; *P*<0.001 Mean ΔmTSS: **A:** +0.27; **B:** 2.44; *P*<0.001 HAQ scores ≤0.5: **A:** 55%; **B:** 39%; *P*<0.001
GUEPARD Trial[25]	Active (DAS28 >5.1), early RA (<6 months) Erosive disease: 34%	**A:** MTX nonescalating n=32 **B:** Adalimumab + MTX n=33	Low DAS28 (<3.2) • Week 12: **A:** 25%; **B:** 64%; *P*=0.001 • Week 52: **A:** 65%; **B:** 64%; *P*=0.98 Mean ΔmTSS • **A:** +1.8±4.7; B: +1.9±4 No radiologic progression • **A:** n=16; **B:** n=14 (No statistics reported)

Table 4. (Cont.) TNF Blocker Therapy — State-of-the-Art Presentations at EULAR 2008

Theme	Patient Population	Treatment/Comparator	Results
NEO-RACO Trial[26]	N=100 active, early RA (≤12 months)	**A:** Infliximab + MTX + SSZ + HCQ + prednisolone vs. **B:** Placebo + MTX + SSZ + HCQ + prednisolone	**2-year follow up** Remission: **A:** 70%; **B:** 53%; *P*=0.08 Sustained remission (6-24 mos): **A:** 40%; **B:** 31%; *P*=0.40 Radiologic progression: Mean ΔSHS: **A:** 0.2; **B:** +1.4; *P*=0.005
Dutch Rheumatoid Arthritis Monitoring (DREAM) Registry Prospective Study[27]	N=169 with DAS28 >3.2	Step-up DMARD scheme MTX x 8 weeks No remission:↑ MTX dose No remission: MTX + SSZ No remission: MTX ↑ + SSZ dose No remission: MTX −SSZ + adalimumab	Median time to first remission: 25 weeks Remission: DAS28 <2.6 • Week 8: 15.5% • Week 12: 22.2% • Week 20: 30.7% • Week 24: 38.8% • Week 36: 52.1% • Week 48-52: 51.0%
Treatment Following Failure of TNF Blockers			
TSCQM Foundation, Swiss Society of Rheumatology Prospective RA Cohort Study[28]	N=300 pts failing primary TNF blocker therapy Reasons for failure: • Lack of efficacy • Other causes — i.e. adverse events	**A:** Alternative TNF blocker n=199 **B:** Rituximab n=101	**6-month follow up** Evolution of DAS28 • Lack of efficacy switch: **A:** 1.03; **B:** 1.55; difference significant (*P*-value not reported) Adverse event switch: **A:** 0.77; **B:** 0.86 • Effects independent of concomitant DMARD therapy or type of TNF blocker
Meta-analysis[29]	Patients switched to alternate TNF blocker: • N=5306 from 31 studies • Literature published 1995-2007 • ACR/EULAR abstracts 2004-2007	Reasons for switch: • Primary efficacy failure (66%) • Intolerance (proportion not specified)	Switch in TNF blockers associated with decreased therapeutic benefit, defined by ACR20-ACR70; DAS28; EULAR (good/moderate); HAQ in patients with primary failure and those with failure on more than 1 agent.

BSR: British Society for Rheumatology; DMARD: disease modifying anti-rheumatic drug; HAQ: health assessment questionnaire; HCQ: hydroxychloroquine; IRR: incidence rate ratio; LFT: liver function test; mTSS: modified total Sharp score; MTX: methotrexate; RR: relative risk; SHS: Sharp/van der Heijde; SMR: standardized mortality ratio; SSZ: sulfasalazine; ULN: upper limit of normal

The results of studies presented at EULAR clearly underscore the long-term benefits of TNF blocker therapy for the treatment of RA. After nearly a decade of use in the clinic, evidence of radiologic benefit and disease remission continues to accumulate.[15-17] Long-term evaluation of adverse events suggests no clear evidence of increased risk of malignancy or mortality with long-term use of TNF blockers.[30-32] In fact, mortality may be reduced. However, as revealed in both earlier studies and subsequent registry analysis, TNF blockers are associated with a significantly increased risk of developing tuberculosis, indicating the continued need for pre-treatment screening and surveillance practices.

Two presentations addressed the management of patients who fail initial TNF blocker therapy.[28,29] Both suggest that switching among TNF blockers may produce modest efficacy returns. Investigators involved in both studies suggest that patients who fail primary therapy with a TNF blocker should be considered as candidates for treatment with a biologic with an alternate mechanism of action.

Emerging TNF Blockers

A series of presentations focused on a preapproval study of the novel TNF blockers certolizumab, a pegylated FC-free anti-TNF agent, and golimumab, a fully human anti-TNF-α MAb **(Table 5)**.

Table 5. Emerging TNF Blockers

Agent	Citation	Clinical Trial/Patient Population	Treatment Comparator	Results
Certolizumab	van Vollenhoven, et al[33]	RAPID 1 and RAPID 2 Trials	Use of ACR-hybrid scores to evaluate efficacy RAPID 1 n=982 RAPID 2 n=619	ACR-hybrid analysis of results supports efficacy of ACR20/ACR50/ACR70 parameters evident in results of the 2 clinical trials
	Emery, et al[34]	RAPID 1 Trial	To evaluate dependency of treatment response on starting dose of MTX	Changes in ACR20 and DAS28 similar across certolizumab treatment groups, regardless of MTX starting dose (10-30 mg/week)
	Keystone, et al[35]	RAPID 1 Trial	Trial N=982, randomized 2:2:1 **A:** Certolizumab 200 mg + MTX **B:** Certolizumab 400 mg + MTX **C:** Placebo + MTX	**52-week follow up** Mean ΔmTSS • **A/B/C:** 0.4/0.2/2.8 ACR20 — differences significant beginning at week 1 of therapy • **A/B/C:** 53.1%/54.9%/13.1% ACR50 • **A/B/C:** 38.0%/39.9%/7.6% ACR70 • **A/B/C:** 21.2%/23.2%/3.5%; *P*≤0.001, all comparisons
	van der Heijde, et al[36]	RAPID 1 and RAPID 2 Trials	RAPID 1 n=276 RAPID 2 n=207 **A:** Certolizumab + MTX **B:** Placebo + MTX Analysis of results in patients with-drawing early (week 16) due to lack of efficacy, defined as failure to achieve ACR20 at both weeks 12 and 14	**Mean ΔmTSS at 16 wks** RAPID 1 • **A:** +0.2±2.2; **B:** +1.0±2.5 RAPID 2 • **A:** +0.2±1.8; **B:** +0.8±2.8 *P*≤0.05, all comparisons
	Landewé, et al[37]	RAPID 2 Trial Radiographic inhibition of structural damage progression	**A:** Certolizumab 200 mg + MTX n=246 **B:** Certolizumab 400 mg + MTX n=246 **C:** Placebo + MTX n=127	**24-week follow up** Mean ΔmTSS • **A/B/C:** +0.2/−0.4/+1.2; *P*≤0.01/*P*≤0.001 for 200 mg/400 mg certolizumab vs. placebo
	Mease, et al[38]	RAPID 1 and RAPID 2 Trials Analysis of adverse events	**A:** Certolizumab 200 mg + MTX **B:** Certolizumab 400 mg + MTX **C:** Placebo + MTX	No significant differences in rates of infection or malignancy, or in incidence of cardiac disorders among treatment groups • Serious infections more frequent in certolizumab-treated pts **A/B/C:** 6.0%/7.1%/1.5% • AEs leading to withdrawal **A/B/C:** 7.2%/7.0%/3.8% *P*-values, significance NR
Golimumab	Keystone, et al[39]	GO-FORWARD Trial Pts with active RA, despite continuing treatment with MTX	N=444 **A:** Placebo + MTX **B:** Golimumab 100 mg + Placebo **C:** Golimumab 50 mg + MTX **D:** Golimumab 100 mg + MTX **Grp 1:** Combined Golimumab + MTX **Grp 2:** Placebo + MTX	**24-week follow up** ACR20/50/70: • **Grp 1:** 59.6%/34.8%/17.4**% • **Grp 2:** 27.8%/13.5%/5.3% *P*<0.001 for all values vs. **Grp 2** except **P<0.01 Median HAQ improvement • **Grp 1/Grp 2:** +0.44/+0.13; *P*<0.001 SAEs • **Grp 1/Grp 2:** 9.0%/2.3%; *P*\-value NR
	Furst, et al[40]	Effect of golimumab on ACD in pts w/RA, psoriatic arthritis or ankylosing spondylitis	**A:** Golimumab + MTX **B:** Placebo + MTX	**24-week follow up** Mean ΔHb mg/dL • **A/B:** 0.8/0.4; *P*=0.014 Pts achieving normal Hb • **A/B:** 48.5%/36.3%; *P*=0.048

ACD: anemia of chronic disease; HAQ: health assessment questionnaire; Hb: hemoglobin; mTSS: modified total Sharp score; MTX: methotrexate; NR: not reported; SAE: serious adverse event

Both certolizumab and golimumab have been combined with MTX. Results have been compared to the effects of placebo plus MTX. Preliminary results of dose-finding and exploratory studies suggest that certolizumab treatment, significantly more effective than placebo, reduces the signs and symptoms of RA and inhibits radiographic progression of disease, regardless of MTX starting dose.[33,34] For golimumab, as with the approved TNF blockers, there is early evidence of improvement in both the clinical and quality of life measures of disease.[39,40] Added to the armamentarium of already-approved TNF blockers, the clinical placement of these agents remains uncertain. Head-to-head clinical trials would be welcome, but are unlikely to be conducted.

State-of-the-Art Results of Tocilizumab Therapy for Rheumatoid Arthritis

A principal player in the cytokine network in RA pathogenesis, IL-6 is a potent proinflammatory cytokine produced in increased amounts in active disease. IL-6 is involved in recruitment of cells into the synovium, activation of fibroblast-like synoviocytes, and maturation of osteoclasts responsible for joint destruction. In addition, IL-6 is a major mediator of systemic inflammation, partly manifesting as increased production of C-reactive protein (CRP), and hepatic hepcidin. Increased levels of these proteins are associated with elevated cardiovascular risk, and the anemia of chronic disease (ACD), respectively.

Tocilizumab is a novel biological agent directed against both the soluble and cell-bound IL-6 receptor. Results from several Phase 2 clinical trials and from one Phase 3 trial provided initial evidence of safety and efficacy in the treatment of RA, either as monotherapy or in combination MTX. Major clinical themes concerning the use of tocilizumab in RA presented at EULAR are summarized in **Table 6**; detailed description of the abstracts appears in **Table 7**.

Table 6. Tocilizumab — Major Clinical Themes Presented at EULAR

Current Results of Phase 3 Clinical Trials
- OPTION/TOWARD Trials — Results in MTX inadequate responders
- AMBITION Trial — Tocilizumab vs. MTX monotherapy
- RADIATE Trial — Treatment of patients failing TNF blocker therapy
- Treatment of early and established RA
- Effects on inflammatory biomarkers

Safety
- Effects on liver enzymes
- Effects on neutrophil numbers

Table 7. Tocilizumab Clinical Trials — State-of-the-Art Presentations at EULAR 2008

Theme/Treatment	Citation	Patients (N)	Results
Use of tocilizumab in MTX inadequate responders **OPTION/TOWARD Trials** **A:** Tocilizumab (8 mg/kg) + DMARDs vs. **B:** Placebo + DMARDs	Gomez-Reino, et al[41]	**A:** n=814 **B:** n=402	**24-week follow up** Week 2 response • EULAR moderate-to-good improvement: **A:** 64%; **B:** 18.4%; *P*-value NR Week 24 response • ACR90 **A:** 5.1% (n=41); **B:** 0.5% (n=2); *P*-value NR ○ Significant improvements in all ACR core parameters in patients treated with tocilizumab ○ EULAR good response: A-40.0%; B-4.4%; *P*<0.0001
	Pooled analysis of pts in trials treated with MTX[42] Beaulieu, et al	**A:** n=1008 **B:** n=617	**24-week follow up** Results at 2 weeks • EULAR moderate-to-good improvement **A:** 64.1%; **B:** 17.2%; *P*<0.0001 • ΔMean CRP (mg/dL) **A:** 2.44; **B:** 0.19 mg/d; *P*<0.0001 • ΔMean Hb (g/dL) **A:** +0.67; **B:** 0.13; *P*<0.0001 Results at 4 weeks • ACR20/ACR50/ACR70 **A:** 34.7%/11.0%/2.9%; **B:** 13.6%/1.8%/0.0%; *P*<0.0001
	Pooled analysis Genovese, et al[43]	**A:** n=1008 **B:** n=617	Results at 24 weeks • ACR20/ACR50/ACR70 **A:** 60.3%/38.9%/20.8%; **B:** 25.1%/9.6%/2.6%; *P*<0.0001 • Significant improvements in all core components of ACR criteria noted

Table 7. (Cont.) Tocilizumab Clinical Trials — State-of-the-Art Presentations at EULAR 2008

Theme/Treatment	Citation	Patients (N)	Results
Use of tocilizumab in MTX inadequate responders **OPTION/TOWARD Trials** **A:** Tocilizumab (8 mg/kg) + DMARDs vs. **B:** Placebo + DMARDs	Pooled analysis Smolen, et al[44]	**A:** n=1008 **B:** n=617	Infections/100 pt-yrs • **A:** 116.6; **B:** 95.5; *P*-values NR Serious infections/100 pt-yrs • **A:** 2.8%; **B:** 1.6% Increase in fasting total cholesterol 200->240 mg/dL • **A:** 5.6%; **B:** 1.0% Non-hematologic neoplasm • **A:** 0.1%; **B:** 0.3% Withdrawal due to AE • **A:** 4.4%; **B:** 2.1% AEs marginally higher in tocilizumab treated pts Tocilizumab safe and well tolerated
	Smolen, et al[45]	Data stratification by age: <65 vs. ≥65 yoa **A:** n=835 **B:** n=510	Differences in efficacy between treatment groups are preserved, regardless of pt age
AMBITION Trial **A:** Tocilizumab monotherapy 8 mg/kg n=286 **B:** Escalating MTX 7.5-20 mg weekly n=284 Active RA No prior failure of MTX or other biologics	Sebba, et al[46]		• All HR-QoL measures showed significant improvement at week 24 • FACIT-Fatigue scores improved in group A as early as week 4 of treatment
	Jones, et al[47]	**24-week follow up** <u>Results at 2 weeks</u> • EULAR moderate-to-good response — **A:** 64%; **B:** 19%; *P*-value NR • Normalized CRP levels in group A pts (data NR) <u>Results at 24 weeks</u> • ACR20/ACR50/ACR70 — **A:** 70%/44%/28%; **B:** 53%/34%/15% *P*-values: ACR20:<0.0001; ACR50:0.0023; ACR70: 0.0002 • ΔCRP (mg/dL): **A:** 2.6; **B:** 1.9 • ΔHb (g/dL): **A:** +1.2; **B:** +0.1 • AE leading to withdrawal — **A:** 3.8%; **B:** 5.3% • Serious AEs/Serious infections: **A:** 4%/3%; **B:** 1.4%/0.7% • ALT >3xULN: **A:** 2%; **B:** 4% • Total cholesterol <200 mg/dL to ≥240 mg/dL: **A:** 13%; **B:** <1%; *P*-values not reported	
RADIATE Trial **A:** Tocilizumab 4 mg/kg+MTX n=161 **B:** Tocilizumab 8 mg/kg+MTX n=170 **C:** Placebo+MTX n=158 **Active RA despite previous TNF blocker therapy**	Emery, et al[48]	**24-week follow up** ACR20/ACR50/ACR70: • **B:** 50.0%/28.8%/12.4%; **C:** 10.1%/3.8%/1.3% *P*<0.0001 ACR20/ACR50; *P*=0.0002 ACR70 EULAR moderate-to-good response: • **B:** 67.7%; **C:** 16.5%; *P*<0.0001 Disease remission (DAS28<2.6) • **B:** 30.1%; **C:** 1.6%; *P*=0.0001	
Treatment of early and established RA	Genovese, et al[49]	Pts with moderate-to-severe early (n=326) or established (n=1298) RA, with inadequate response to prior DMARD therapy **A:** Tocilizumab + DMARDs vs. **B:** Placebo + DMARDs	**24-week follow up** ACR20/ACR50/ACR70 • Early RA — **A:** 59.9%/40.1%/23.8%; **B:** 27.4%/10.5%/1.6%; *P*<0.0001 • Established RA — **A:** 60.5%/38.6%/20.1% B:24.5%/9.3%/2.8%; *P*<0.0001 Disease remission (DAS28 <2.6) • Early RA — **A:** 38.3%; **B:** 2.2%; *P*<0.0001 • Established RA — **A:** 27.5%; **B:** 2.8%; *P*<0.0001 EULAR moderate-to-good response • Early RA — **A:** 80.7%; **B:** 37.9% *P*<0.0001 • Established RA — **A:** 79.4%; **B:** 36.3% *P*<0.0001

Table 7. (Cont.) Tocilizumab Clinical Trials — State-of-the-Art Presentations at EULAR 2008

Theme/Treatment	Citation	Patients (N)	Results
Effects on inflammatory biomarkers **Pooled data from OPTION, TOWARD, RADIATE, AMBITION**	Levi, et al[50]	**A:** Tocilizumab (4 or 8 mg/kg) as monotherapy or + DMARD n=1410 **B:** Placebo + DMARD n=833	**24-week follow up** • Correlation of tocilizumab exposure (AUC) with levels of CRP, ESR and SAA • AUC exposure levels (x10^3 h.µg/mL) ◦ Low (n=201) — <100 ◦ Medium (n=539) — 100-200 ◦ High (n=670) - ≥200 • Increasing tocilizumab exposure associated with decreased levels of all biomarkers, especially CRP
Effects on liver enzymes **OPTION/TOWARD analysis**	Beaulieu, et al[51]	**A:** Tocilizumab n=1008 **B:** Placebo n=618 • Majority of elevations (not specified) <3x ULN • No pt on tocilizumab experienced simultaneous >3x ULN increases in AST/ALT plus bilirubin	Pts w/ALT-AST >3x<5xULN • AST: **A:** 3.9%/1.4%; **B:** <1%/<1% • ALT: **A:** 6.8%/4.5%; **B:** 3.4%/<1% *P*-values NR Dose interruption • **A:** 1.9/3.4%; **B:** 0.7/1.5%; *P*-values NR ◦ Normalization of liver enzyme tests occurred in 1/3-1/2 pts who continued tocilizumab therapy ◦ Discontinuation of therapy associated with return to baseline ◦ No clinical signs/symptoms of liver injury
Effects on neutrophils OPTION/ TOWARD analysis	Smolen, et al[52]	**A:** n=1008 **B:** n=618	Serious infections • **A:** 2.8%; **B:** 1.6%; *P*-values NR • Neutrophil counts >LLN in 92.1% of pts who developed serious infection

AE: adverse events; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin; HR-QoL: health related quality of life; LLN: lower limit of normal; NR: not reported; SAA: serum amyloid A; ULN: upper limit of normal

Discussion was focused mainly on analysis of clinical data from the OPTION and TOWARD trials, which enrolled patients with inadequate response to MTX. Rapid improvement in efficacy endpoints over the first two weeks of treatment with tocilizumab were noted.[41,42] Moreover, the differences were significant when compared to results from patients treated with placebo plus MTX, and occurred to an equivalent degree in patients with early or established disease, and in patients older than 65 years of age.[45,49]

While tocilizumab has been described as being safe and generally well tolerated, adverse events occurred with marginally higher frequency among tocilizumab treated patients.[45] There was a notable disruption of liver enzyme levels, with numerically higher incidences of tocilizumab treated patients experiencing elevations in ALT and AST of 3-to-5-fold the upper limit of normal.[51] However, liver enzyme levels did normalize in up to one-half of patients who continued therapy, and no clinical signs of liver injury were reported. Results of the AMBITION trial (see below) failed to detect a notable association between highly elevated liver enzyme levels and tocilizumab treatment.[47]

In one analysis, serious infection occurred more frequently among tocilizumab treated patients. However, neutrophil counts were above the lower limit of normal in 92.1% of patients who developed serious infection, suggesting lack of association between these two parameters.[52]

The AMBITION trial explored the potential for tocilizumab monotherapy in patients with active RA who had not failed MTX therapy, and had not been previously treated with biologics. The rapid response to tocilizumab was corroborated by the results of this study, in which a significant difference in FACIT-Fatigue scores developed as early as 4 weeks following initiation of treatment.[46] Results at 24 weeks of follow up demonstrated significant improvement in ACR20/ACR50/ACR70 and EULAR moderate-to-good responses, as well as all quality of life measures.[46,47]

Interestingly, results of the AMBITION trial provided evidence of normalization of CRP, a principal marker of systemic inflammation.[47] These data were corroborated by pooled analysis of the OPTION, TOWARD, AMBITION and RADIATE tocilizumab clinical trials.[50] Investigators concluded that increased levels of tocilizumab exposure are associated with normalization of CRP levels between infusions.

Potential of Tocilizumab for Rheumatoid Arthritis Treatment

The clinical potential of tocilizumab for the treatment of RA may be evaluated by examining critical study parameters against those existing at the time of studies of TNF blockers at a similar stage of development. In the absence of head-to-head clinical trials, patient demographic factors, clinical endpoints, and DMARD combinations should all be considered in the placement of tocilizumab into the treatment armamentarium. Efficacy and safety must be balanced against nonbiologic DMARD therapy, particularly MTX, and therapy with both established and emerging TNF blockers.

Table 8. Evaluating Tocilizumab for the Treatment of RA

Criteria	TNF Blockers Initial Development 1990-1999	Tocilizumab Initial Development 2000-2007
Patient Selection • Disease duration • Disease severity	• 6-10 years • Severe disease	• ≤2 years • Use dictated by ± response to MTX • Moderate-to-severe disease
Primary response to DMARDs • Nonbiologic (MTX) • Biologic (TNF blockers)	• Insufficient response to MTX ○ N/A	• Insufficient response to MTX • Tocilizumab results to be interpreted in context of trials conducted to evaluate switch among TNF blockers
Endpoints	• Primary: ACR20 • Secondary: ACR50, ACR70 • Inhibition of progression of structural joint damage • TEMPO — etanercept • Adalimumab (Keystone)	• Primary: ACR20 • Secondary: ACR50, ACR70 • DAS28 • Disease remission (DAS28 <2.6) • Inhibition of progression of structural joint damage
Combination with DMARDs	• +MTX; investigation of MTX dosing and schedule • Monotherapy	• +MTX • Monotherapy
Results	• RR to achieve therapeutic response with any TNF blocker=1.81 (95% CI 1.43-2.29)[15] • NNT for ACR20/ACR50/ACR70=3/4/8 for any TNF blocker + MTX vs. MTX alone[15] • NNH=27; side effects more prevalent in patients receiving TNF blockers[15]	• Good ACR20/ACR50/ACR70 responses against placebo + MTX treatment groups • Potential clinical impact of rapid normalization of systemic inflammatory markers should be systematically evaluated • Insufficient data on radiographic progression of disease to date • Safety data suggest careful monitoring of liver function and neutrophil counts is required

NNH: number needed to harm; NNT: number needed to treat

Several parameters should be considered when evaluating the potential role of tocilizumab in the RA treatment armamentarium **(Table 8)**.

While it is not possible to directly compare the results of studies of TNF blockers and tocilizumab, there are some noteworthy trends, summarized in **Table 8**. As a result of the evidence of favorable efficacy and safety profiles of TNF blockers, there has been a tendency to use biologics, and to recruit patients to trials of emerging biologic therapies, earlier in the disease history. It is hoped that early treatment will prevent or at least significantly delay joint erosion, with a tolerable adverse events burden. To this end, relevant endpoints in current clinical trials include the systematic evaluation of radiographic parameters of disease, as well as the evaluation of clinical disease remission.

Initial trials of TNF blockers enrolled patients with severe disease, as evaluated by clinical and quality of life criteria.[15] In the most recent meta-analysis, 8/12 cited studies of TNF blockers were performed in patients with insufficient response to MTX. While tocilizumab trials have been similarly designed, the evidence of diminishing responsiveness following switching among TNF blockers should be considered when evaluating the use of emerging biologics.[28,29]

Results of a recent meta-analysis clearly demonstrate the benefits of TNF blocker therapy for the treatment of RA. Original trials focused on ACR20 response rates. It is now recognized that markers of radiologic progression of disease are an important component of evaluating the efficacy of new biologics. In addition, changes in systemic markers of inflammation, and the potential clinical consequences, should also be monitored.

For tocilizumab, the preliminary efficacy data available from the four most recent clinical trials (OPTION/TOWARD/AMBITION/RADIATE) are promising. However, further information is required concerning the radiologic progression of disease. The significance and potential benefits of normalization of systemic inflammation, while intriguing, are presently unclear. Currently, there is no evidence of long-term adverse consequences of intermittently elevated liver enzymes or reduced neutrophil counts associated with tocilizumab treatment. However, careful monitoring of patients on therapy will be required.

Conclusions

Over the past decade, TNF blockers have provided the bulk of biologic treatment for the management of RA. The 2008 EULAR update provides evidence of promising long-term efficacy and safety results, underscoring the clinical utility of these agents. However, evidence of diminishing response among patients who fail primary treatment with TNF blockers suggests a place for biologics with alternative mechanisms of action in the armamentarium. Evidence of the efficacy and safety of agents that target alternative cytokines in the proinflammatory network, including the IL-6R antagonist tocilizumab, expand and strengthen the biologic approach to the management of RA.

Several important questions remain. Optimal combinations of biologic and nonbiologic DMARDs must be more fully identified through focused clinical investigation. Ideally, selection of drug combinations should be made on the basis of head-to-head clinical trials and reliable predictors of response, which requires the identification of appropriate biomarkers and pharmacogenomic indicators.

Disease remission is the standard measured clinical response to antirheumatic therapy. However, progress in treating RA with the biologic DMARDs, particularly at earlier stages of disease, invites redefinition of treatment response. While a combination of clinical and radiographic criteria may be more informative than clinical response alone, there is no clear recommendation of how to proceed in case of divergent results.

The trend to earlier treatment with biologics requires continued investigation. In one study of 120 patients with early RA, induction therapy with infliximab plus methotrexate resulted in successful cessation of the TNF blocker in 56% of patients within a year.[53] However, disease flare mandated resumed therapy in 10 patients, and an additional 30 patients failed to develop a primary response. Clearly, the role of induction therapy needs to be better established.

Once appropriately defined, the treatment responsive patient also poses an interesting challenge. Should MTX or biologics — or both — be withdrawn in patients who respond to treatment? If so, at what point following the determination of response? On the other hand, in patients who fail to respond to TNF blockers, how long should we persist with therapy, through either dose adjustment or switching of agents, before we consider alternative therapies?

Finally, we must confront the challenge posed by clinical trial design. Results obtained with emerging biologics typically are evaluated against combinations of placebo and MTX. Given the proven clinical profile of the TNF blockers, is this an appropriate control group? Once again, we are faced with making treatment decisions without the benefit of meaningfully comparative clinical trials.

Despite the many questions that remain, we continue to make progress in diagnosing RA and in managing risk for disease progression. The development and investigation of new treatment agents may be expected to grow as our understanding of the articular and systemic basis of RA pathophysiology increases.

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