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Do biologics-naïve patients with rheumatoid arthritis respond better to tocilizumab than patients for whom anti-TNF agents have failed? A retrospective study

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ABSTRACT

Objective. *To determine responses to tocilizumab between patients with rheumatoid arthritis (RA) who switched to anti-TNF agents and those who are biologics-naïve.*

Methods. *This retrospective study investigated 107 patients with RA who were treated with tocilizumab. At baseline, 61 of them had already been treated with anti-TNF agents (switched group; 46 for inefficacy and 15 for adverse events), and 46 were biologics-naïve (naïve group). Treatment responses to tocilizumab at week 12 and 24 were compared between the switched and naïve groups using the disease activity score 28 (DAS28).*

Results. *Forty-two (91.3%) and 50 (82.0%) patients in the naïve and switched groups, respectively, completed 24 weeks of tocilizumab treatment. The DAS28-ESR and DAS28-CRP values (means±SD) at weeks 12 and 24 compared to baseline decreased significantly for the naïve and switched groups. The DAS28-ESR and DAS28-CRP values at weeks 12 and 24 were significantly decreased in the naïve group, compared to the switched group. Disease activity was improved in the naïve patients compared to the switched patients.*

Conclusions. *Tocilizumab was safe, tolerable, and clinically effective for patients with inadequate responses to anti-TNF therapy and for those who were biologics-naïve, and it was more effective among the latter.*

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by persistent synovitis and progressive destruction of cartilage and bone. RA is also associated with systemic inflammatory manifestations as well as the local inflammation of several joints. Biological agents targeting tumour necrosis factor (TNF) have recently been successful in treating RA (1-4). However, 20–40% of patients have inadequate responses to these agents, and novel therapeutic interventions with new modes of action are urgently required to treat RA. Several reports have suggested that patients can benefit from a second course of therapy with a different anti-TNF agent after a first attempt has failed (5-8).

Interleukin-6 (IL-6) is a proinflammatory cytokine that is abundantly expressed and detectable in the joints and circulation of patients during the active phases of RA (9, 10). The IL-6 signal is mediated via 80-kDa IL-6 receptors (IL-6Rs) on the cell surface or the soluble form of IL-6R (sIL-6R). Tocilizumab is a humanised anti-human IL-6R monoclonal antibody (Mab) that inhibits the binding of IL-6 to IL-6R or sIL-6R (11).

However, the clinical benefit and safety of switching from another anti-TNF agent to tocilizumab have not been defined. Furthermore, the responses of patients who switched from anti-TNF agents and of those whose initial therapy is tocilizumab have not been compared. This study compares the effectiveness of tocilizumab between patients with RA who switched from anti-TNF agents and those who are biologics-naïve.

Patients and methods

Inclusion and exclusion criteria

All patients commencing tocilizumab therapy for RA at our institution from April 2008 to March 2010 (n=107) were reviewed retrospectively. All patients fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA with a history of treatment failure with at least one disease-modifying anti-rheumatic drug (DMARD), or anti-TNF agent. Exclusion criteria consisted of compliance with the contraindications and precautions provided by the manufacturer of tocilizumab.

Study design

All patients started infusions of 8 mg/kg (body weight) of tocilizumab every four weeks for a total of 24 weeks. Patients could receive concomitant corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and DMARDs both before and during the study. No instructions were given regarding dose alterations of concomitant RA medication during the study. Concomitant medication remained stable throughout the study for most patients.

Table I. Baseline characteristics of patients.

	Naïve n=46	Switched n=61	*p*-value
Sex (male/female)	11/35	8/53	0.1479
Age (yrs)	60.1 ± 11.5	57.6 ± 13.0	0.2842
Disease duration (yrs)	6.6 ± 8.9	8.2 ± 6.7	0.0082
Weight (kg)	57.0 ± 8.7	54.1 ± 9.9	0.1077
Stage (I/II/III/IV)	1/14/28/3	0/11/39/11	0.0256
Class (1/2/3/4)	2/31/13/0	0/45/16/0	0.8984
Tender joint count	5.3 ± 5.2	5.9 ± 6.4	1.0000
Swollen joint count	5.4 ± 5.1	6.1 ± 5.6	0.5069
ESR (mm/h)	38.9 ± 28.6	41.6 ± 31.0	0.6709
Patient global assessment	44.2 ± 25.3	58.3 ± 29.3	0.0129
CRP (mg/dl)	2.0 ± 2.2	2.6 ± 2.9	0.4335
DAS28-ESR	4.6 ± 1.4	5.0 ± 1.5	0.3356
DAS28-CRP	4.1 ± 1.3	4.5 ± 1.5	0.2611

Data are expressed as mean±S.D.; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS: disease activity score.

Table II. Assessment of tocilizumab safety.

	Naïve (n=46)	Switched (n=61)
No. of patients of continuous (%)	42 (91.3)	50 (82.0)
Total adverse events	31 in 26 pts	54 in 33 pts
Hearth failure		1 †
Tachycardia	1 †	
General malaise		1 *
Vomiting	1	
Common cold	1 *	2 (*1)
Vertigo	1 †	
Stomatitis	2	1
Cystitis1		
Increased blood pressure	1	
Rash		1
Increased cholesterol	14	22
Liver anormality	8	15 (†1)
Decreased leukocyte count	4	8

*Temporary postponement; †Withdrawal from study.

Assessment of effectiveness

The findings of baseline clinical assessments are summarised in Table I. Disease activity was assessed by the same rheumatologist on day 0 (baseline), and at 12 and 24 weeks thereafter. Clinical responses to therapy were evaluated using the disease activity score (DAS) 28 (high disease activity, >5.1; moderate disease activity, >3.2 to ≤5.1; low disease activity, ≤3.2; remission, <2.6). The last observation carried forward (LOCF) was applied at weeks 12and 24 when patients discontinued treatment or when data were unavailable.

Safety assessment

Safety assessments included physical examinations, pre- and post-dose electrocardiograms, and laboratory analyses of hematology, serum biochemistry, coagulation, immunologic parameters and urine. Adverse events were recorded throughout the study.

Statistical analysis

Differences between the groups in terms of counts of swollen and tender joints, patient global assessment (PGA), ESR, CRP and DAS28 scores were assessed using the Chi-square test. A *p*-value below 0.05 denotes a statistically significant difference.

Results

Patients' characteristics

One hundred and seven patients were treated with tocilizumab. Sixty-one of them had already been treated with anti-TNF agents (switched group) and 46 patients started tocilizumab as initial biological agent therapy (naïve group). In 61 patients who switched from anti-TNF therapy to tocilizumab, 46 patients were due to lack of drug efficacy (switched for inefficacy group) and 15 patients were due to following the development of adverse events (switched for AE group).

The baseline characteristics revealed that more patients had a longer duration of RA, an increased patient global assessment and RA stage in the switched, than in the naïve group, significantly. However, differences between other values did not reach statistical significance (Table I).

Safety

A total of 85 adverse events (including abnormal laboratory profiles) occurred in all of 59 patients analysed for safety. Twenty-six and 33 patients in the naïve and switched groups described 31 and 54 adverse events, respectively (Table II). The incidences of patients with adverse events were 56.5% (26 of 46 patients) and 54.1% (33 of 61 patients), respectively. Most of the adverse events that arose in both groups were mild or moderate. Four patients (switched, n=3; naïve, n=1) discontinued tocilizumab due to serious adverse events comprising cardiovascular complications (switched, n=1; naïve, n=1), vertigo (switched, n=1) and liver abnormality (switched, n=1). Three other patients (switched, n=2; naïve, n=1) temporarily postponed tocilizumab therapy due to upper respiratory infection (common cold) or general malaise.

Clinical effect

The baseline values of inflammatory indicators (ESR, CRP), disease activity (tender and swollen joint count, PGA), and DAS28 are shown in Table I and the data presented in Table III shows that they time-dependently decreased. These values were significantly decreased at weeks 12 and 24 compared to baseline in both groups. The mean DAS28-ESR and DAS28-CRP values at baseline did not significantly differ between the groups, whereas those at weeks 12 and 24 were significantly decreased in the naïve, compared to the switched group.

Table III. Changes in disease activity measures of all patients with RA before and after tocilizumab for 12 and 24 weeks.

	Naïve (n=46)			Switched (n=61)		
Week	0	12	24	0	12	24
TJC	5.3 ± 5.2	1.9 ± 2.5†	2.0 ± 3.4†	5.9 ± 6.4	3.9 ± 4.9*†	3.2 ± 4.3*†
SJC	5.4 ± 5.1	2.3 ± 4.3†	1.7 ± 2.2†	6.1 ± 5.6	4.5 ± 5.2*	3.4 ± 4.4†
ESR (mm/h)	38.9 ± 28.6	4.8 ± 4.7†	5.1 ± 5.2†	41.6 ± 31.0	12.2 ± 18.8*†	11.0 ± 18.7*†
CRP (mg/dl)	2.0 ± 2.2	0.3 ± 1.4†	0.3 ± 1.4†	2.6 ± 2.9	0.5 ± 2.1†	0.5 ± 2.0†
PGA	44.2 ± 25.3	31.3 ± 24.0†	27.5 ± 21.5†	58.3 ± 29.3*	35.4 ± 26.1†	32.8 ± 25.1†
DAS28-ESR	4.6 ± 1.4	2.1 ± 1.1†	2.1 ± 1.2†	5.0 ± 1.5	3.2 ± 1.5*†	2.8 ± 1.5*†
DAS28-CRP	4.1 ± 1.3	2.4 ± 1.0†	2.2 ± 1.0†	4.5 ± 1.5	3.0 ± 1.3*†	2.8 ± 1.3*†
DAS28-ESR activity, (Pts no.)						
Remission	0 (0)	65.2 (30)	69.6 (32)	0 (0)	39.3 (24)	52.5 (32)
Low	15.2 (7)	21.7 (10)	15.2 (7)	13.1 (8)	24.6 (15)	18.0 (11)
Moderate	43.5 (20)	10.9 (5)	13.0 (6)	41.0 (25)	23.0 (14)	21.3 (13)
High	41.3 (19)	2.2 (1)	2.2 (1)	45.9 (28)	13.1 (8)	2.8 (5)

	Switched for inefficacy (n=46)			Switched for adverse event (n=15)		
Week	0	12	24	0	12	24
TJC	6.1 ± 6,8	4,2 ± 5,3**†	3.6 ± 4.7†	5.3 ± 5.3	2.8 ± 3.1	2.1 ± 2.6†
SJC	5.8 ± 5.1	4.7 ± 5.5**	3.5 ± 4.6†	6.9 ± 7.0	4.0 ± 4.2	3.3 ± 4.0†
ESR (mm/h)	44.3 ± 32.2	10.4 ± 16.3†	11.0 ± 18.7**†	33.2 ± 26.3	11.5 ± 24.2†	12.7 ± 25.2†
CRP (mg/dl)	2.7 ± 3.1	0.6 ± 2.5†	0.5 ± 2.2†	2.3 ± 1.8	0.3 ± 1.0†	0.3 ± 1.0†
PGA	61.8 ± 28.6*	38.1 ± 26.3†	34.4 ± 24,4†	47,7 ± 29.9	27.3 ± 24.7†	28.2 ± 27.4†
DAS28-ESR	5.1 ± 1.5	3.4 ± 1.5**†	2.9 ± 1.6**†	4.6 ± 1.3	2,7 ± 1.3†	2.5 ± 1.3†
DAS28-CRP	4.5 ± 1.5	3.1 ± 1.3**†	2.9 ± 1.3**†	4.4 ± 1.4	2.7 ± 1.2†	2.5 ± 1.2†
DAS28-ESR activity, % (no. pts)						
Remission	0 (0)	37.0 (17)	47.8 (22)	0 (0)	46.7 (7)	66.7 (10)
Low	13.0 (6)	23.9 (11)	17.4 (8)	13.3 (2)	26.7 (4)	20.0 (3)
Moderate	41.3 (19)	23.9 (11)	26,1 (12)	40.0 (6)	20.0 (3)	6.7 (1)
High	45.7 (21)	15.2 (7)	8.7 (4)	46.7 (7)	6.7 (1)	6.7 (1)

Data are expressed as mean±S.D.; no. pts.: number of patients; TJC: tender joint count; SJC: swollen joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PGA: patient global assessment; DAS: disease activity score.
†*vs*. week 0; $p<0.05$, *Naive *vs*. Switched; $p<0.05$, **Naive *vs*. Switched for inefficacy; $p<0.05$.

Then, the clinical assessments were evaluated in the three groups (naïve, switched for inefficacy and switched for adverse events (AE)). The mean DAS28-ESR and DAS28-CRP values at weeks 12 and 24 were low in order of the naïve, the switched for AE and the switched for inefficacy group. Those at weeks 12 and 24 significantly decreased in the naïve, compared to the switched for inefficacy group, and not significantly compared to the switched for adverse events (AE) group.

Among the therapeutic outcomes of tocilizumab using the EULAR response criteria, the ratios (%) of good responses at week 24 were 69.5% (32 patients), 50.0% (23 patients) and 60.0% (9 patients) in the naïve group, the switched for inefficacy group and the switched for AE group, respectively. The incidence of a good response was higher in the naïve, than in the switched group. Disease activity was improved more and remission rates were better in order of the naïve, the switched for AE and the switched for inefficacy group (Table III).

The continuation rates for tocilizumab therapy were 91.3% (42/46 patients), 80.4% (37/46 patients) and 86.6% (13/15 patients) in the naïve, switched for inefficacy groups and switched for AE groups, respectively.

These results suggested that tocilizumab is more effective for patients who are biologics-naïve, than for those who switch from other anti-TNF therapies.

Discussion

The constitutive overproduction of IL-6, a pleiotropic cytokine that regulates the immune response, as well as inflammation, haematopoiesis and bone metabolism, is thought to play a pathological role in RA (12). The excessive production of IL-6 augments the autoimmune reaction and causes systemic inflammatory manifestations. Interleukin-6 in the presence of soluble IL-6 receptors induces osteoclast differentiation and can be responsible for the joint destruction and osteoporosis associated with RA (13).

This retrospective study compared the clinical effect and safety of tocilizumab therapy between patients who had previously undergone anti-TNF therapy (switched group) and those who had not (naïve group).

Many adverse events developed in both groups; almost all were mild and tolerable and the incidence was the same as that reported (14). Tolerance of tocilizumab therapy was good and the compliance rate of patients under tocilizumab therapy was > 80% in both groups.

Our comparative retrospective study adds to existing knowledge by providing evidence that tocilizumab reduces disease activity in biologics-naïve pa-

tients and in those who switch from anti-TNF therapies. DAS28 value, EULAR response and remission rates had improved, and the continuation rates for tocilizumab therapy were better in the order of the naïve, the switched for AE and the switched for inefficacy group. The EULAR 2009 recommendations indicate that patients who do not respond to an initial TNF inhibitor should receive a different TNF inhibitor, abatacept, rituximab, or tocilizumab. The responses of our patients confirmed that IL-6 plays an important role in the development of RA and indicated that tocilizumab may be administered as a first line biologic.

However, it is clear that old age, longer disease duration, more structure damage and decreased function are associated with poorer responses to anti-TNF therapy (15). In this study, the small difference in disease duration and stage between the groups may be poor responses to therapy in the switched group of patients.

Further studies are therefore required to determine the long-term safety and therapeutic effect of tocilizumab as well as the feasibility of preventing joint damage in patients with RA.

Conclusion

Our results suggest that tocilizumab is a safe and effective treatment option for some patients even when anti-TNF therapy has been ineffective, and that it is more effective for patients who are biologics-naïve. A targeted blockade of IL-6 signalling is a highly effective and promising means of decreasing RA disease activity.

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