Research article

Certolizumab effect in a cohort of 60 Libyan patients with rheumatic diseases

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Abstract

Background: Tumour Necrosis Factor (TNF) has a central role in the pathogenesis of Rheumatoid Arthritis (RA), mediating both inflammation and joint damage. Certolizumab Pegol (CZP) is a PEGylated Fab fragment of a humanized anti-TNF antibody with high affinity to TNF.

Objective: The study was done to monitor the effects and side effects of certolizumab on our Libyan patients with rheumatic diseases.

Methods: The inclusion criteria for the study were all patients with rheumatic diseases who were treated by certolizumab in the period from August 2014 to August 2016 in Rheumatology Department, Tripoli Medical Center, Tripoli, Libya. They were 60 patients, 43 of them had RA, 14 patients had Ankylosing Spondylitis (AS), 2 patients had Psoriatic Arthropathy (PsA) and 1 patient had enteropathic arthritis. Certolizumab 400mg subcutaneous was given at week 0, 2, 4 and then 400mg every 4 weeks. Demographic details such as age and sex were recorded. Clinical characteristics as rheumatoid factor in RA patients, disease duration, duration of taking certolizumab and drugs used before starting certolizumab were noted. Assessment of disease activity was measured by DAS28 for RA patients, by BASDAI for AS patients and by DAPsA for PsA patients. For all patients, complete blood count, erythrocyte sedimentation rate, liver function test, hepatitis screen, urine routine examination and tuberculin test before starting certolizumab were requested to monitor its side effects during follow up.

Results: Forty three patients had rheumatoid arthritis, their mean age was 44.6±SD10.67 years, 11.6% were male and 88.3% were female. Rheumatoid factor was positive in 58%, negative in 19% and unknown in 23%. Fourteen patients were ankylosing spondylitis; their mean age was 34.9±SD8.22 years, 85.7% were male and 14.2% were female. Two patients had psoriatic arthritis, mean age was 43.5±SD16.26 years, one was female and the other was male. One patient had enteropathic arthritis; she was a female aged 57 years. All RA patients were on prednisolone and/or one or two DMARD before starting CZP and failed to show response. All AS patients were on one or two NSAIDs and/or salazopyrine and failed to show response before starting CZP. One psoriatic arthritis patient was on leflunomide and methotrexate (MTX) and the other was on MTX alone. Enteropathic arthritis patient was on MTX, azathioprine and salazopyrine. The mean of DAS28 before starting CZP for RA patients was 4.9±SD1.15 and the mean of DAS28 at the last dose was 3.1±SD1.12 (P value<0.0001). The mean of BASDAI before using CZP was 4.2±SD1.61 and the mean of BASDAI at the last dose was 1.7±SD1.86 (P value <0.0012). Both PsA patients had moderate disease activity (mean of DAPsA=20±SD1.6) and became (mean of DAPsA=6±SD1.2) which means low disease activity (P value <0.0002). Enteropathic arthritis patients showed significant improvement regarding gastrointestinal symptoms and arthritis. Regarding side effects of certolizumab pegol, one female RA patient developed tuberculus lymphadenitis and one male RA patient had hypersensitivity reaction.

Conclusion: During two years of follow up of our rheumatic diseased patients on certolizumab, we noticed a significant improvement in disease activity scores with minimal side effects.

Introduction

Tumour Necrosis Factor (TNF) has a central role in the pathogenesis of Rheumatoid Arthritis (RA), mediating both inflammation and joint damage[1-3]. TNF inhibitors revolutionised the management of RA because these agents improve signs and symptoms and physical function and inhibit structural damage, particularly in combination with methotrexate (MTX) [4-7].

Certolizumab Pegol (CZP) is a PEGylated Fab fragment of a humanized anti-TNF antibody with high affinity to TNF. It lacks an Fc region and may thus avoid potential Fc-mediated effects such as complement- or antibody-dependent, cell-mediated cytotoxicity, which have been seen *in vitro*, and attachment of the PEG moiety to the Fab fragment yield a molecule with a plasma half-life of about 2 weeks[8].

Certolizumab pegol gained FDA approval in September/October 2013 for two new indications, adult with active Psoriatic Arthritis (PsA) and adult with active Ankylosing Spondylitis (AS)[9]. It was already approved for adults with Crohn's disease and rheumatoid arthritis[9].

Under current ASAS/The European League Against Rheumatism (EULAR) recommendations, Non-Steroidal Anti-Inflammatory Drugs (NSAID) are the first-line treatment option for axial spondyloarthritis patients[10]. In patients with inadequate response to ≥ 2 NSAIDs for ≥ 4 weeks in total, TNF inhibitor therapy is recommended for AS patients[11-18].

Materials and Methods

The inclusion criteria for the study were all patients with rheumatic diseases who were treated by certolizumab in the period from August 2014 to August 2016 in Rheumatology Department, Tripoli Medical Center, Tripoli, Libya. They were 60 patients, 43 of them had RA, 14 patients had AS, 2 patients had PsA and 1 patient had enteropathic arthritis.

All patients consented to participate in the study. The study was done after receiving consent from the Tripoli Medical Center ethical and research committee.

Certolizumab 400mg subcutaneous was given at week 0, 2, 4 and then 400mg every 4 weeks. Demographic details such as age and sex were recorded. Clinical characteristics as rheumatoid factor in RA patients, disease duration, duration of taking certolizumab and drugs used before starting certolizumab were noted. Assessment of disease activity was measured by DAS28 for RA patients, by BASDAI for AS patients and by DAPSA for PsA patients. Disease activity scores were measured at the start of certolizumab and every injection thereafter.

For all patients, complete blood count, erythrocyte sedimentation rate, liver function test, hepatitis screen, urine routine examination and tuberculin test before starting certolizumab were requested to monitor its side effects during follow up.

Data was analysed using SPSS computer software package. The mean and standard deviations of the age, disease duration and duration of taking certolizumab were calculated. P value to measure if there is significant difference between the means of DAS28, BASDAI or DAPSA (according to the patient either RA, AS or PsA) at the start of certolizumab and at the last follow up were calculated using t-test.

Results

All patients with rheumatic diseases who took CZP in the period between August 2014 and August 2016 were included in the study. Forty three patients had rheumatoid arthritis, their mean age was 44.6±SD10.67 years, 11.6% were male and 88.3% were female. Rheumatoid factor was positive in 58%, negative in 19% and unknown in 23%. Fourteen patients had ankylosing spondylitis; their mean age was 34.9±SD8.22 years, 85.7% were male and 14.2% were female. Two patients had psoriatic arthritis, mean age was 43.5±SD16.26 years, one was female and the other was male. One patient had enteropathic arthritis; she was a female aged 57 years.

The mean duration of rheumatic diseases and the mean duration of taking CZP are shown in Table 1. All RA patients were on prednisolone and/or one or two DMARD before starting CZP and failed to show response. All AS patients were on one or two NSAIDs and/or salazopyrine and failed to show response before starting CZP.

Table 1: Mean duration of rheumatic diseases and the mean duration of taking Certolizumab pegol (CZP)

No. of patients (n=60)	Mean of disease duration	Mean duration of taking CZP
RA (43 patients)	7.3±SD3.34 years	10.46±SD 2.60 months
AS (14 patients)	7±SD2.7 years	16.07±SD 3.08 months
PsA (2 patients)	2±SD1.18 years	7.5±SD1.45 months
Enteropathic arthritis (1 patient)	Duration=2 years	Duration=6 months

One psoriatic arthritis patient was on leflunomide and methotrexate (MTX) and the other was on MTX alone. Enteropathic arthritis patient was on MTX, azathioprine and salazopyrine. Table 2 shows different rheumatic diseases and different drug regimens used for them. The mean of DAS28 before starting CZP for RA patients was 4.9±SD1.15 and the mean of DAS28 at the last dose was 3.1±SD1.12.

Table 2: Shows different rheumatic diseases and different drug regimens used for them

Drug regimen	No. of patients
Rheumatoid arthritis patients	Total n=43 patients
Methotrexate MTX alone	16
MTX+ Hydroxychloroquine HCQ	8
MTX+ Salazopyrine SZP	3
HCQ alone	4
Prednisolone alone	1
SZP alone	1
Leflunomide alone	6
Leflunomide+ SZP	2
MTX+ leflunomide	2
Ankylosing spondylitis patients	Total n=14 patients
NSAID	12
Salazopyrine	2
Psoriatic arthritis patients	Total n=2 patients
Leflunomide+ MTX	1
MTX alone	1
Enteropathic arthritis patient	One patient
Azathioprine+ Salazopyrine + MTX	1

P-value showed extremely statistically significant difference between the two means which was (P value<0.0001). The mean of BASDAI before using CZP was 4.2±SD1.61 and the mean of BASDAI at the last dose was 1.7±SD1.86. These results showed a very statistically significant difference between the two means P value <0.0012. Both PsA patients had moderate disease activity (mean of DAPsA=20±SD1.6) and became (mean of DAPsA=6±SD1.2) which means low disease activity (P value <0.0002) (Table 3).

Table 3: Activity scores of different rheumatic diseases at start and at the last dose of certolizumab

Type of rheumatic disease	At start of certolizumab	At last dose	P value
RA Mean of DAS28	4.9± SD1.15	3.1± SD1.12	< 0.0001
AS Mean of BASDAI	4.2±SD1.61	1.7± SD1.86	< 0.0012
PsA Mean of DAPsA	20± SD2.6	6±SD1.2	< 0.02

Enteropathic arthritis patients showed significant improvement regarding gastrointestinal symptoms and arthritis. Regarding side effects of certolizumab pegol, one female RA patient developed tuberculus lymphadenitis at the fifth dose of CZP and one male RA patient had hypersensitivity reaction after the first dose.

Discussion

Certolizumab pegol is a PEGylated humanized Fab monoclonal antibody that targets and neutralizes both membrane bound and soluble tumour necrosis factor preventing inflammation and consequently the destruction of cartilage and bone[19]. Interestingly the Fc portion, which is lacking in CZP, is not necessary for TNF inhibitor to be clinically effective in RA. Thus, the primary mode of action of TNF inhibitor in RA does not appear to involve Fc-mediated effect but rather the binding and inactivation of TNF and probably reverse signalling which can also be mediated by Fc–free Fab molecule[20,21].

Certolizumab pegol has a relatively long elimination half-life of two weeks, allowing subcutaneous administration once every two or four weeks[19]. Certolizumab pegol provided rapid, significant and clinically meaningful improvement in physical function and quality of life, with significant changes in HAQ-DI at week 1 and week 12, which continued to improve through to week 24[22].

As functional outcomes are associated with structural damage in progressive RA, treatments as CZP that can both improve physical function and inhibit joint damage may help prevent long-term disability[23-25].

Treatment with certolizumab pegol plus methotrexate were associated with significant greater improvement in DAS28 from baseline versus placebo at all time points (p<0.001)[22]. In our patients with RA a significant improvement in DAS28 at the start of treatment and the last dose was observed (p<0.0001).

Landewe *et al*[26], observed that at week 12, statistically significant higher proportion of patients in certolizumab 200mg every 2 weeks (57.7%) and certolizumab 400mg every 4 weeks group (63.6%) achieved an ASAS20 response compared with placebo (38.3%) (P= 0.004 and p< 0.001) respectively. Landewe *et al*[26] also noted that certolizumab treatment resulted in significant improvement in BASFI, BASDAI and BASMI linear versus placebo (p<0.001) and improvement in BASFI, BASDAI and BASMI linear were similar between certolizumab treatment arms and observed from week 1[26].

In our study the mean of BASDAI of our patients at the start of certolizumab was 4.2± SD 1.6 and BASDAI at last close was 1.7 ± SD 1.86, this difference between the two means was very statistically significant P<0.0012. Certolizumab pegol had an acceptable safety profile with a low incidence of discontinuation due to adverse events[22]. Serious infections, including tuberculosis were reported more frequently with certolizumab pegol than placebo, consistent with rates associated with other anti- TNF treatment[27]. In our study tuberculosis was recorded in one patient (1.6%) and hypersensitivity reaction occurred in one patient (1.6%) indicating high safety profile of certolizumab.

Conclusion

During two years of follow up of our rheumatic diseased patients on certolizumab, we noticed a significant improvement in disease activity scores with minimal side effects.

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