AB0194

ASSOCIATION OF MALNUTRITION WITH QUALITY OF LIFE IN ELDERLY RA PATIENTS

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Background: Rheumatoid arthritis (RA) is a progressive joint condition that leads to joints destruction and complications in the internal organs and significantly affects the a patient's functional ability. Elderly patients with RA complain of pain, mood and sleep disturbances, fatigue, and insomnia in addition to weakness, decreased appetite and weight loss. Chronic use of medications results in the risk of comorbidities and decreased physical functioning. All this together significantly contributes to a negative assessment of quality of life (QoL).

Objectives: Due to the chronic nature of RA and the high risk of malnutrition in this group of patients, an attempt was made to assess the QoL, activities of daily living and severity of frailty syndrome according to the results of the MNA questionnaire in a group of elderly patients with RA.

Methods: The study included 98 patients (age over 60 years) with a diagnosis of RA according to ARA. Standardized tools were used in the study: the WHO-QOL-BREF to assess quality of life, the Edmonton Frailty Scale to assess frailty syndrome, MNA to assess nutritional status and MMSE to assess cognitive function. Medical data were taken from the hospital records.

Results: Patients significantly differed in the extent of limitations in basic (ADL) and advanced activities of daily living (IADL) according to their nutritional status. The higher the level of malnutrition, the greater the limitations of undertaken activities. In addition, an adverse effect of reduced body weight on the occurrence of cognitive dysfunction was observed (33.33% of malnourished patients were diagnosed with dementia vs. 1.79% in normal weight patients). Similarly, frailty syndrome or vulnerability to frailty syndrome was associated with malnourished patients (33.3% mild, 16.67% moderate, and 16.67% severe frailty syndrome). Malnourished patients had significantly lower QoL scores in all domains of the WHOQOL-BREF questionnaire compared to normal weight patients and multivariate analysis of the effect of selected variables on QoL in the domains of the WHOQOL-BREF questionnaire showed that a significant independent determinant of lower QoL in all domains was the presence of frailty syndrome, respectively: Perception of QoL (R=-0.069), Self-perception of health (R=-0.172), Physical domain (R=-0.425), Psychological domain (R=-0.432), Social domain (R=-0.415), Environmental domain (R=-0.317). Malnutrition was a significant independent determinant of QoL in the self-perception of health domain (R=-0.08). Additionally, in the regression analysis, a positive effect of male gender was observed on the assessment of QoL in the psychological (R=1.414) and environmental (R=1.123) domains.

Table 5. Comparative analysis of quality of life in terms of each domain of the WHOQOL-BREF questionnaire according to nutritional status.

WHOQOL BREF	MNA			p
	Malnutrition (Mean±SD)	Risk of malnutrition (Mean±SD)	Normal nutrition (Mean±SD)	
Perception of quality of life	3,33±1,03	3,33±0,68	3,68±0,58	0,029
Self-perception of health	2,67±0,82	2,47±0,84	3,14±0,98	0,004
Physical health	10,83±3,49	11,31±2,39	12,68±2,27	0,02
Psychological domain	12,5±3,89	13,28±2,73	14,45±2,24	0,056
Social domain	12,33±2,86	12,67±2,93	14,29±2,61	0,007
Environmental domain	13,83±2,86	13,22±2,28	13,96±2,17	0,34

Conclusion: Malnourished people have a lower quality of life than people of normal weight. Malnutrition is a factor that negatively affects daily functioning, cognitive functioning, and the severity of frailty syndrome. A significant independent determinant of reduced quality of life across all domains of the WHOQOL-BREF questionnaire is frailty syndrome.

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2021-eular.4297

Rheumatoid arthritis - biological DMARDs

AB0195

PHARMACOKINETIC AND PHARMACODYNAMIC EVALUATION OF A PROPOSED BIOSIMILAR MSB11456 VERSUS BOTH THE US-LICENSED AND EU-APPROVED TOCILIZUMAB: RESULTS OF A RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, SINGLE-DOSE TRIAL IN HEALTHY ADULTS

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Background: Tocilizumab, a biologic disease-modifying antirheumatic drug, is a recombinant humanized monoclonal immunoglobulin G1 antibody against the interleukin-6 receptor (IL-6R). MSB11456 is a proposed biosimilar to the US-licensed tocilizumab and EU-approved tocilizumab. Prior to initiation of its clinical development program, MSB11456 was considered highly similar to the reference products based on extensive *in vitro* pharmacological testing and functional activity assays.

Objectives: This double-blind, parallel-group phase I study (NCT03282851) assessed the pharmacokinetic (PK) and pharmacodynamic (PD) equivalence of MSB11456 to US-licensed and EU-approved tocilizumab and provided data on the similarity of safety profiles and immunogenicity of MSB11456 and the reference products in healthy adult subjects.

Methods: Healthy adult volunteers were randomized to receive a single 162 mg subcutaneous injection of MSB11456, US-licensed tocilizumab, or EU-approved tocilizumab. Samples for PK/PD and immunogenicity analysis were taken pre-dose, up to 29 days postdose, and at the end of study visit (day 48). Primary endpoint PK parameters were natural log transformed and analyzed using analysis of covariance (ANCOVA) methods; results were then transformed back to the original scale. Secondary PD analysis measured serum soluble IL-6R and serum C reactive protein (sCRP) parameters, and data were analyzed using a method similar to that for PK data. Safety data were collected throughout the study and analyzed descriptively.

Results: 685 subjects were randomized and treated. Results of the primary PK analysis demonstrated bioequivalence between MSB11456 and both US-licensed and EU-approved tocilizumab, as well as between the reference products, since all corresponding 90% confidence intervals (CIs) for the geometric least squares mean (LSM) ratios were within the predefined 80.00% to 125.00% equivalence margin (Table 1). PD analyses also demonstrated equivalence of MSB11456 and both US-licensed and EU-approved tocilizumab, as well as between the reference products. Safety, tolerability and immunogenicity were also comparable between treatments. The incidence of tocilizumab-specific neutralizing antibodies was low (<3% for all three products).

Conclusion: PK and PD equivalence of MSB11456, US-licensed tocilizumab, and EU-approved tocilizumab were demonstrated with comparable immunogenicity, safety, and tolerability for the three products. This study adds to the totality of evidence in support of MSB11456 as a proposed biosimilar to tocilizumab.

Table 1. Results of primary PK analysis

Parameter	Treatment	n	Ratio of geometric LSMs (%)	90% CI of ratio
<i>MSB11456 vs US-licensed tocilizumab</i>				
AUC _{0-∞}	MSB11456	194	106.16	96.80, 116.43
	US-licensed tocilizumab	190		
AUC _{0-t}	MSB11456	230	104.15	93.58, 115.90
	US-licensed tocilizumab	226		
C _{max}	MSB11456	230	104.45	95.05, 114.77
	US-licensed tocilizumab	226		
<i>MSB11456 vs EU-tocilizumab</i>				
AUC _{0-∞}	MSB11456	194	104.03	94.96, 113.96
	EU-approved tocilizumab	200		
AUC _{0-t}	MSB11456	230	94.78	85.15, 105.50
	EU-approved tocilizumab	224		
C _{max}	MSB11456	230	94.83	86.28, 104.22
	EU-approved tocilizumab	224		
<i>US-licensed vs EU-approved tocilizumab</i>				
AUC _{0-∞}	US-licensed tocilizumab	190	97.99	89.40, 107.41
	EU-approved tocilizumab	200		
AUC _{0-t}	US-licensed tocilizumab	226	91.01	81.71, 101.36
	EU-approved tocilizumab	224		
C _{max}	US-licensed tocilizumab	226	90.79	82.57, 99.84
	EU-approved tocilizumab	224		

AUC, area under the serum concentration-time curve (µg·h/mL); AUC_{0-∞}, AUC from time zero to infinity; AUC_{0-t}, AUC from time zero to the time of the last quantifiable concentration; C_{max}, maximum concentration (µg/mL)

Acknowledgements: Medical writing support was provided by Caroline Spencer and Dr Sue Chambers (Rx Communications, Mold, UK), funded by Fresenius Kabi SwissBioSim.

Disclosure of Interests: Christian Schwabe: None declared, Chris Wynne: None declared, Andras Illes Employee of: Fresenius Kabi SwissBioSim, Martin Ullmann Employee of: Fresenius Kabi SwissBioSim, Emmanuelle Vincent Employee of: Fresenius Kabi SwissBioSim, Vishal Ghorl Employee of: Fresenius Kabi SwissBioSim, Corinne Petit-Frere Employee of: Biosimilars, Fresenius Kabi SwissBioSim, Anne-Sophie Racault Employee of: Fresenius Kabi SwissBioSim, Isabelle Morin Employee of: Former employee of Fresenius Kabi SwissBioSim
DOI: 10.1136/annrheumdis-2021-eular.74

AB0196

SURVIVAL ANALYSIS OF TIME TO FIRST ADVERSE DRUG REACTION AND DRUG SURVIVAL IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH ADALIMUMAB AND ETANERCEPT

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Background: Treatment of rheumatoid arthritis (RA) with biologic disease-modifying antirheumatic drugs (bDMARDs) has been common practice in the last two decades. However, differences in patients experiencing adverse drug reactions (ADRs) between individual bDMARDs, such as adalimumab (ADA) and etanercept (ETN), during first time treatment has not been studied yet in real-world settings.

Objectives: To compare proportions of RA patients experiencing ADRs as well as survival to first ADR and drug survival during treatment with ADA and ETN.

Methods: Retrospective single centre cohort study including adult patients with RA, treated with either ADA or ETN between 1 January 2003 and 30 April 2020. The proportions of patients experiencing an ADR were compared by assessing the percentage of patients, treated with either ADA or ETN, experiencing at least one ADR during their first time treatment. Survival to first ADR and drug survival were assessed by calculating time between start of treatment and first ADR and start of treatment and discontinuation of treatment respectively. Stop and restart of treatment within 90 days was considered as continuous use. Differences in proportions were statistically tested using Fisher's Exact Test. Differences in drug survival between ADA and ETN were tested by Kaplan-Meier analysis and Log Rank tests.

Results: A total of 422 patients were included in this study (ADA 259, ETN 163). For 93 patients (21.2%) an ADR was registered during first time treatment. The proportion of patients experiencing at least one ADR during their first time treatment was 22.7% for ADA and 20.2% for ETN ($p=0.628$). Survival time to first ADR did not differ significantly between ADA and ETN (median survival ADA 10.34 years (95% CI [7.62-13.06], median survival ETN not reached, $p=0.109$, figure 1A). Median drug survival was 1.75 years for ADA (95% CI [1.38-2.11]) and 2.68 years for ETN (95% CI [1.73-3.64]). Drug survival differed significantly ($p<0.001$, figure 1B).

Figure 1. Kaplan-Meier survival curves for adalimumab and etanercept with (a) survival to first ADR and (b) drug survival.

Conclusion: Neither the proportion of patients experiencing ADRs nor survival to first ADR during first time treatment with ADA and ETN differed significantly. Drug survival of first time drug treatment of ADA was significantly lower compared to drug survival of first time drug treatment of ETN.

Disclosure of Interests: My Nguyen: None declared, Kimberly Velthuis: None declared, Joep Scholl: None declared, Jurriaan Jansen: None declared, Leanne Kosse: None declared, Peter ten Klooster: None declared, Naomi Jessurun: None declared, Harald Vonkeman Consultant of: BMS, Celgene, Celltrion, Galapagos, Gilead, Janssen-Cilag, Lilly, Novartis, Pfizer, Sanofi-Genzyme, Grant/research support from: Abbvie

DOI: 10.1136/annrheumdis-2021-eular.179

AB0197

EFFICACY AND SAFETY OF HLX01 COMBINED WITH METHOTREXATE IN CHINESE PATIENTS WITH MODERATELY TO SEVERELY ACTIVE RHEUMATOID ARTHRITIS WHO HAD INADEQUATE RESPONSES TO METHOTREXATE: RESULTS OF A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY

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Background: Rituximab is an effective therapy for rheumatoid arthritis (RA) patients with inadequate responses to methotrexate (MTX)^{1,2}. However, it has not been registered or approved in China for the treatment of RA by far. HLX01, an approved rituximab biosimilar (demonstrated in Chinese patients with diffuse large B-cell lymphoma)³, is thus evaluated in this study for the benefits of Chinese RA patients.

Objectives: This study aimed to evaluate the efficacy and safety of HLX01 plus MTX versus placebo plus MTX in Chinese patients with active RA who had inadequate responses to MTX.

Methods: This was a randomised, double-blind, placebo-controlled phase 3 study conducted in China (NCT03522415). Eligible patients were randomised 2:1 to receive intravenous infusion of 2x1000mg HLX01 or placebo on day 1 and day 15. Patients with inadequate responses at week 16 and 20 were allowed to receive rescue treatments. Patients were retreated with or switched to receive (if initially assigned to placebo) 2x1000mg rituximab at the first day of week 24 and 26. The primary endpoint of this study was the American College of Rheumatology criteria (ACR) 20 response at week 24. Secondary efficacy endpoints were evaluated at week 12, 24, 36 and 48. The safety, pharmacokinetics, pharmacodynamics and immunogenicity of HLX01 were observed and analyzed throughout the study.

Results: Between May 28, 2018 and Sep 11, 2020, a total of 275 patients (ITT set) were randomised and 263 patients without major protocol deviations were included in per-protocol set (PPS). At week 24, HLX01 showed statistically superior efficacy ($p<0.001$) to placebo (ACR20: 60.7% vs 35.9% in ITT set, 60.3% vs 37.1% in PPS). Secondary efficacy endpoints were also significantly improved in HLX01 group compared with placebo (Table 1). The overall incidence of serious treatment emergent adverse events (TEAEs), adverse drug reactions (ADRs), and TEAEs leading to drug discontinuation were similar among treatment groups, with the most common TEAE been upper respiratory tract infection before (18.1% vs 18.5%) or after (13.0% vs 12.3%) week 24. Serum concentrations, immunogenicity and pharmacodynamics were similar between HLX01 and placebo groups.