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AB0475

THE INFLUENCE OF SWITCHING FROM ETANERCEPT ORIGINATOR TO ITS BIOSIMILAR ON EFFECTIVENESS AND THE IMPACT OF SHARED DECISION MAKING ON RETENTION AND WITHDRAWAL RATES

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Background: With biological patents expiring, biosimilars are becoming a realistic, less costly alternative to their originator. The data from numerous randomised clinical trials support that it is safe, effective and cost saving to switch to a biosimilar. However, real world data about efficacy, safety, and cost-effectiveness of such a switch are lacking.

Since shared decision making (SDM) is a key factor in the treatment of rheumatic diseases, a non-mandatory open label transitioning from Etanercept originator to its biosimilar was performed at the rheumatology department of Bernhoven.

Objectives: The first goal of this study was to investigate the effect of switching from Etanercept originator to its biosimilar on the effectiveness of treatment. The second aim was to analyse the effect of SDM on the 1 year retention rates and reasons for withdrawal in daily clinical practice.

Methods: All patients with rheumatoid arthritis (RA), axial spondyloarthritis (SpA) and psoriatic arthritis (PsA) that were using Etanercept originator between 01–06–2016 and 23–10–2017 were informed by letter of the possibility to switch to its biosimilar. During the next outpatient visit with their rheumatologist the possibility to switch was discussed. Patients had the opportunity to ask questions regarding biosimilars and the switch to a biosimilar. If patients agreed the switch was made, with the reservation that they could switch back to the originator if they encountered difficulties with the biosimilar.

Using the registry of the rheumatology department at Bernhoven data were collected on disease activity (DA), medication use and adverse events from the moment of switch till 23–10–2017. As measure for DA the DAS28 was used for RA and PsA, the ASDAS was used for SpA. Stop reasons for biosimilars were verified using the health record system of the hospital. Reasons for change in disease activity and discontinuation of biosimilar treatment were assessed.

Results: Between 01–06–2016 and 23–10–2017 80% (69 patients) of the Etanercept originator users switched to its biosimilar. These patients switched to biosimilar after a median time of 5.1 (IQR 2.8–8.3) years. By 23–10–2017, median follow-up of 307 (IQR 196–357) days, the mean DA did not significantly differ from the DA at baseline, 3.1 (95%>CI 2.5–3.7) vs. 2.8 (95%>CI 2.5–3.1). At end of follow-up 25% of the patients had discontinued their treatment and either switched back to originator (18%), switched to another biological (3%) or stopped treatment with biologicals (4%).

Reasons for switching back to originator were adverse events (58%), lack of effect (17%) and “adverse event and lack of effect” (25%). Only one serious adverse event was reported. This was a drug hypersensitivity reaction. After the patient was recovered, the originator was restarted without any difficulties.

Conclusions: An open label non-mandatory switch from Etanercept originator to its biosimilar showed that around 80% of the patients is willing to perform this switch. Switching did not affect effectiveness of treatment during one year follow-up. 75% of the patients were able to continue biosimilar therapy. In the 69 patients that switched only one serious adverse effect occurred.

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AB0476

THE EFFICACY OF IMMUNOADSORPTION WITH INFliximab THERAPY ON THE MODULATION OF DISEASE ACTIVITY IN PATIENTS WITH SEVERE RHEUMATOID ARTHRITIS

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Background: Active refractory rheumatoid arthritis (RA) is common in real-world. Patients with active refractory RA usually have poor prognosis. And they respond poorly to a variety of therapies. The arrival of remission or low disease activity

(LDA) as soon as possible is an important way to improve their prognosis. We investigated the effectiveness of immunoadsorption therapy, a novel blood purification treatment, as a rapid and sustained disease-modifying therapy for active refractory RA.

Objectives: To evaluate the efficacy of additional immunoadsorption therapy (2 times) besides infliximab (IFX) on disease remission in patients with active refractory RA.

Methods: 90 patients with severe RA were included in this study. 43 patients were treated with basic IFX 3 mg/kg+methotrexate (MTX) therapy, and other different 47 patients, besides of basic therapy, were previous given 2 times additional immunoadsorption therapy. IFX 3 mg/kg was infused at weeks 0, 2, 6, 14, 22 and 30. Age, sex ratio, mean disease duration and core index of disease activity in two treatment groups were collected at weeks 0, 2, 6 and 30 weeks to compare the efficacy and safety of combined immunosorbent therapy in the treatment of severe RA.

Results: The baseline age, sex ratio and core indexes of disease activity were comparable between the two treatment groups ($p>0.05$). After treatment, the core indexes of disease activity of all patients decreased significantly compared with their baseline levels ($p<0.05$). The degree of reduction in the combined therapy group was significantly better than that in the basic treatment group ($p<0.05$), and the proportion of ACR remission patients in the combined treatment group was higher than that in the basic treatment group at different stages after treatment.

Conclusions: Additional immunoadsorption therapy can rapid relieve the disease activity of severe RA patients, and the remission rate of 30 W was significantly higher than only IFX treatment. However, due to the limited sample size of this study, the efficacy of additional immunoadsorption needs further observations.

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AB0477

INHIBITION OF LARGE JOINT DESTRUCTION IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH TOCILIZUMAB

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Background: Rheumatoid arthritis (RA) causes not only inflammation of small joints, such as hands and feet, but also inflammation of large joints. Destruction of large joints is correlated with impairments of physical activity in RA patients more than destruction of small joints is ⁽¹⁾. We experience strong inhibitory effect of inflammation in synovial joints, not only small joints but also large joints, by treatment with tocilizumab (TCZ), an antibody to IL-6 receptor in RA patients in daily clinical practice. Although inhibitory effects of small joint destruction by TCZ is well known, inhibitory effects of large joint destruction is unknown.

Objectives: This retrospective study investigated inhibitory effect of large joint destruction by TCZ treatment in RA patients.

Methods: Toyohashi RA database (TRAD) was used. TCZ was initiated in 65 RA patients in our institute. 31 cases (23 female and 8 male) who continued TCZ over 2 years were utilised in this study. Baseline characteristics and time course of disease activity were investigated. Delta-modified Sharp score (Δ mTSS) per year was used to evaluate small joint destruction. ARASHI score ⁽²⁾ was used to evaluate large joints destruction. Shoulders, elbows, hips, knees and ankles were evaluated using ARASHI score.

Results: Treatment continuation rate of TCZ was 86.3% at one year and 77.7% at two years in whole 65 cases (Kaplan-Meier methods). Baseline characteristics of 31 cases was as followed. Average age: 56 years old. Average RA duration: 6.6 years. Concomitant rate of MTX: 74.2%. Concomitant rate of prednisolone:

64.5%. Order of TCZ: 1st biologics in 9 cases, 2nd biologics in 9 cases, 3rd biologics in 13 cases. Rates of symptomatic joints (pain or swelling): 45.1% in shoulders, 44.6% in elbows, 0.0% in hips, 51.9% in knees and 37.7% in ankles. Average CDAI was 23.3 at baseline, 6.8 at one year and 5.0 at two years. Average Δ mTSS was 8.1 at baseline, 2.7 from baseline to one year and 1.1 from one year to two years. Evaluation using ARASHI change score from baseline to two years was as followed [worsened, not changed, improved (%)]. Shoulders (51 joints) [9.8, 86.3, 3.9]. Elbows (56 joints) [12.5, 73.2, 14.3]. Hips (53 joints) [0, 94.3, 5.7]. Knees (52 joints) [9.6, 65.4, 25.0]. Ankles (53 joints) [3.8, 91.6, 5.7]. Joint surgery was not performed in evaluated joints during study periods. Influence of symptoms at baseline on large joint destruction: There was a significant difference between ARASHI change score in symptomatic knee joints and that in non-symptomatic joints (-0.5 vs. 0.1 , $p < 0.01$).

Abstract AB0477 – Figure 1. Evaluation of large joint destruction using ARASHI score during two-year tocilizumab treatment

Conclusions: Over 90% of large joints was not destructed during two-year TCZ treatment. Improvement was frequently observed in knees and elbows. Major reasons of improvement of joint destruction were stabilisation of joints by osteophyte formation and repair of bone erosions.

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Rheumatoid arthritis – non biologic treatment and small molecules

AB0478

MILD AND MODERATE HEPATIC IMPAIRMENT HAVE NO CLINICALLY RELEVANT IMPACT ON UPADACITINIB PHARMACOKINETICS: RESULTS FROM A DEDICATED PHASE 1 STUDY

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Background: Upadacitinib is a selective Janus kinase 1 (JAK1) inhibitor being developed for the treatment of several inflammatory diseases, including rheumatoid arthritis (RA). Upadacitinib efficacy was demonstrated in Phase 2 studies in RA, Crohn's disease, atopic dermatitis, in addition to three completed Phase 3 trials in RA. Upadacitinib is a non-sensitive substrate for hepatic metabolism by cytochrome P450 3A; however, 38% and 24% of upadacitinib immediate-release dose are eliminated unchanged in faeces and urine, respectively. Since, there is a potential for upadacitinib use in some patients with hepatic impairment, evaluation of impact of hepatic impairment on upadacitinib exposure is of key clinical relevance. Doses of 15 mg and 30 mg once daily (QD) using upadacitinib extended-release formulation have been evaluated in Phase 3 trials in RA.

Objectives: To evaluate the effect of mild and moderate hepatic impairment on the pharmacokinetics of upadacitinib.

Methods: This was a Phase 1, open-label study in subjects with mild ($n=6$) or moderate ($n=6$) hepatic impairment, according to the Child-Pugh classification, and demographically-matched healthy subjects ($n=6$). Subjects received a single 15 mg dose of upadacitinib extended-release formulation under fasting conditions. Blood samples for upadacitinib assay were collected over 120 hours after administration. Upadacitinib maximum observed plasma concentration (C_{max}), area under the plasma concentration curve (AUC), and terminal phase elimination half-life ($t_{1/2}$) were calculated using non-compartmental analyses. Analyses of covariance were conducted to estimate upadacitinib exposure in subjects with hepatic impairment relative to subjects with normal hepatic function.

Results: There was no statistically significant difference in upadacitinib C_{max} or AUC in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function. One subject with moderate hepatic impairment showed significantly lower upadacitinib exposures than subjects with normal hepatic functions and was excluded as an outlier to ensure a conservative estimate for effect of hepatic impairment on exposure. Upadacitinib exposure ratio central values [and 90% confidence intervals] in subjects with mild and moderate hepatic impairment were 1.28 [0.91–1.79] and 1.24 [0.87–1.76] for AUC and 1.04 [0.77–1.39] and 1.43 [1.05–1.95] for C_{max} , respectively, compared to subjects with normal hepatic function. Upadacitinib terminal elimination half-life (harmonic mean $\pm$ pseudo standard deviation) was 7.99 ± 4.60 and 4.14 ± 1.46 in subjects with mild and moderate hepatic impairment relative to 8.93 ± 4.87 in subjects with normal hepatic function. Upadacitinib was generally well tolerated by the subjects in the study.

Conclusions: Mild and moderate hepatic impairment result in only a very limited effect on upadacitinib plasma exposures ($<30\%$ increase in upadacitinib AUC). Therefore, in clinical trials, dose adjustments in subjects with mild or moderate hepatic impairment are not warranted.

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AB0479

CHARACTERISATION OF THE EFFECT OF RENAL IMPAIRMENT ON UPADACITINIB PHARMACOKINETICS

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Background: Upadacitinib is a selective inhibitor of Janus kinase 1 (JAK1) which is currently being evaluated for the treatment of several autoimmune disorders, including rheumatoid arthritis (RA). Although renal elimination plays a minor role in upadacitinib clearance ($<20\%$ of upadacitinib dose is eliminated unchanged in urine), a considerable number of RA patients have renal dysfunction. As such, characterisation of the effect of different degrees of renal impairment on upadacitinib plasma exposures is important for this patient population.

Objectives: The objective of this study was to assess the pharmacokinetics of upadacitinib in subjects with mild, moderate, and severe renal impairment compared to subjects with normal renal function.

Methods: This Phase 1 study was conducted in 24 adult subjects, who were assigned to one of four groups (six subjects per group) according to the estimated glomerular filtration rate (eGFR) as calculated by the Modification of Diet in Renal Disease (MDRD) equation: normal renal function (eGFR of ≥ 90 mL/min/1.73 m²), mild renal impairment (60–89 mL/min/1.73 m²), moderate renal impairment (30–59 mL/min/1.73 m²), and severe renal impairment (15–29 mL/min/1.73 m²). Subjects received a single 15 mg dose of upadacitinib extended-release formulation under fasting conditions. Blood samples for pharmacokinetic assessments were collected for 120 hours after dosing. The effect of renal impairment on upadacitinib plasma exposures was assessed through regression analysis as well as analysis of covariance across the renal impairment categories.

Results: The point estimates for upadacitinib plasma exposure ratios [90% confidence interval] in subjects with mild, moderate, and severe renal impairment were 1.18 [1.06–1.32], 1.33 [1.11–1.59], and 1.44 [1.14–1.82] for AUC and 1.06 [0.92–1.23], 1.11 [0.88–1.40], and 1.14 [0.84–1.56] for C_{max} , respectively, relative to subjects with normal renal function. In this analysis, one subject with moderate renal function showed exposures significantly lower than subjects with normal