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PREDICTIVE FACTORS FOR REMISSION ACHIEVEMENT BY TOCILIZUMAB MONOTHERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS AFTER INADEQUATE RESPONSE TO METHOTREXATE: A POST HOC ANALYSIS OF THE SURPRISE STUDY

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Background: Interleukin (IL)-6 pathway inhibitors are suggested by European League Against Rheumatism recommendations to have some advantages in rheumatoid arthritis (RA) patients who are not suitable to use methotrexate as comedication compared with other biological disease-modifying antirheumatic drugs. However, it remains to be elucidated what predicts remission achievement by IL-6 pathway inhibitor monotherapy.

Objectives: To identify predictive factors for clinical and structural remission by tocilizumab without methotrexate in patients with RA.

Methods: This is a post hoc analysis of the SURPRISE study, a 2-year randomized, controlled study comparing the efficacy of tocilizumab with (ADD-ON) and without methotrexate (SWITCH) in active RA patients despite methotrexate therapy. The primary endpoint was the DAS28-ESR remission (< 2.6) at week 24. The change in modified total Sharp score from baseline to week 52 (Δ mTSS/year) was also assessed as an endpoint. The effect of clinical parameters, including serum levels of CRP, IL-6, serum amyloid A (SAA), MMP-3, RF and IgG at baseline, on the achievement of DAS28 remission at week 24 was estimated by logistic regression analysis. Multivariate analysis was performed after adjusting for age, gender, height, body weight, body mass index, disease duration, the dose of glucocorticoids, and that of methotrexate.

Results: In SWITCH (n = 96), CRP, SAA, RF and DAS28 at baseline showed predictive value for DAS28 remission at week 24 in univariate analysis. Multivariate analysis confirmed SAA, RF and DAS28 at baseline, but not CRP, as predictive factors, with SAA having the highest value (OR [95%CI] by decrease of 5.0 μ g/mL = 1.011 [1.002-1.020], p = 0.01, ROC-AUC = 0.731). SAA of < 50.0 μ g/mL showed extremely high predictive value for DAS28 remission (OR [95%CI] = 6.012 [1.997-18.096], p = 0.0008, ROC-AUC = 0.761). Furthermore, structural remission (Δ mTSS/year < 0.5) rate at week 52 was significantly higher in patients with SAA of < 50.0 μ g/mL than those with SAA of $\geq$ 50.0 μ g/mL (71% vs 51%, p = 0.048). In contrast, in ADD-ON (n = 98), only DAS28 at baseline showed predictive value for DAS28 remission at week 24 in both univariate and multivariate analysis. In patients with SAA < 50.0 μ g/mL, both DAS28 remission (75% vs 77%, p = 0.79) and structural remission (71% vs 68%, p = 0.71) rate were comparable between SWITCH and ADD-ON.

Conclusion: SAA levels at baseline can predict the necessity of concomitant methotrexate in tocilizumab initiation in patients with RA. Patients with low levels of SAA at baseline may benefit similarly from tocilizumab therapy with and without methotrexate in terms of achieving clinical and structural remission.

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TOWARDS THE LOWEST EFFICACIOUS DOSE (TOLEDO): RESULTS OF A MULTICENTER NON-INFERIORITY RANDOMIZED OPEN-LABEL CONTROLLED TRIAL ASSESSING TOCILIZUMAB OR ABATACEPT INJECTION SPACING IN RHEUMATOID ARTHRITIS PATIENTS IN REMISSION

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Background: Biologic Disease Modifying Anti-Rheumatic Drugs (bDMARD) tapering is possible in rheumatoid arthritis (RA) patients in sustained remission. However, only minimal data are available on progressive tapering of non-TNF bDMARD such as tocilizumab (TCZ) or abatacept (ABA).

Objectives: The TOLEDO (Towards the Lowest Efficacious Dose) trial aimed to assess the impact on disease activity of progressive spacing of TCZ or ABA in RA patients in sustained remission compared to their maintenance at full dose.

Methods: In this multicenter open-label non-inferiority randomized controlled trial, patients fulfilling ACR-EULAR 2010 criteria for RA were included if they were 1) treated with ABA or TCZ for ≥ 1 year (monotherapy or in combination with csDMARD, corticosteroid allowed at a dose ≤ 5 mg/day), 2) in DAS28VS remission (DAS28 <2.6) for ≥ 6 months and 3) with no X-ray damage progression in the year before inclusion. They were randomized into 2 arms: TCZ or ABA maintenance at full dose or DAS28-driven progressive injection spacing arm adapted in which bDMARD IV or SC injections were progressively spaced out every 3 months according to a predetermined 4-step algorithm up to bDMARD discontinuation at step 4. Spacing was reversed to the previous interval in case of relapse. The primary outcome was the evolution of disease activity according to DAS44 during the 2-year follow-up, which

was analyzed with a linear mixed-effect model. Relapse and durable relapse rates (respectively defined as DAS28 > 3.2 , and DAS28 >3.2 not recovered at the following visit despite bDMARD escalation at previous step) were also compared between the 2 arms. Analysis were done per protocol (PP) according to a non-inferiority hypothesis (non-inferiority margin at 0.25 for DAS44 and 0.07 for relapse rates).

Results: 117 patients were randomized in Spacing arm and 116 in Maintenance arm (90 and 112 respectively for PP analysis). 165 (72.4%) patients were treated with TCZ and 63 (27.6%) with ABA. At the end of the follow-up in the Spacing arm, 12.4% of patients were able to discontinue their bDMARD (step 4), 38.9% had tapered them (step 1 to 3) and 23.9% needed to go back to initial step (step 0). In terms of disease activity, the non-inferiority of the Spacing strategy in terms of disease activity (DAS44) was not demonstrated for the whole population and the ABA subgroups: slope difference of 11% (95% CI: -9%, 32%) and 37% (95% CI: -4%, 77%) respectively. However, it was satisfied for the TCZ subgroup: slope difference 3% (95% CI: -21%, 27%) (Figure 1). Relapses (Figure 2) were more frequent in the Spacing arm: +45% (95% CI: 32%, 57%), +48% (95% CI: 24%, 71%) and +43% (95%CI: 29%, 58%) in the whole population, ABA and TCZ subgroups respectively. Durable relapses were more frequent in the Spacing arm: +10% (95%CI: 0%, 19%), 16% (95%CI: -5%, 37%) and 7% (95%CI: -3%, 16%) in the whole population, ABA and TCZ subgroups respectively, compared with Maintenance arm.

Conclusion: The TOLEDO trial generally failed to demonstrate the non-inferiority of the proposed tapering strategy in comparison to maintenance at full dose. However, the non-inferiority was satisfied in terms of disease activity for the TCZ subgroup.

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