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„The investigation of disease outcome in patients with inflammatory bowel diseases on biological therapy with measurement of anti-TNF and anti-TNF-antibodies serum levels: a multicenter, prospective clinical study"

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During the 3 years of the research period we have performed and published several multicenter projects to assess the efficacy , safety of biosimilar infliximab therapy and investigated the value of TDM in predicting clinical outcomes in participating Hungarian IBD centers (central ethical approval was obtained from TUKEB). Blood samples for measuring anti-TNF trough levels and antidrug antibody levels were collected serially or at the time of suspected loss of response (LOR). Several abstracts abstracts have been accepted for oral, digital oral presentation and poster presentation at international congresses in the field of gastroenterology – at ECCO, DDW and UEGW. In the first study –preliminary clinical and immunogenicity data were published already as full article-, we evaluated the data of 210 consecutive IBD patients therapy in a multicenter, prospective, nationwide cohort in the first 30 weeks of biosimilar infliximab therapy (JCC D1,Q1). Clinical response and remission rates and biochemical response were assessed. Clinical remission was achieved in 53.6% of the CD and 59%, 58.6% of the UC patients by week 14. Clinical remission at week 14 was significantly higher in both CD and UC patients who were infliximab naïve. At week 30, 53.4% of the week 14 responder CD patients and 68% of the week 14 responder UC patients were in clinical remission. Immunogenicity was also measured serially. A preliminary rate of trough level and antidrug antibodies was published. The rate of ADA positivity was 4% at week 0 and 16.7% at week 14 in anti TNF naïve and 24.2% at week 0 and 38.5% at week 14 in anti TNF exposed CD patients. In UC, the ADA positivity was 3.6% at week 0 and 21.9% at week 14 in anti-TNF naïve and 30.8% at week 0 and 30% at week 14 in previously infliximab-exposed patients. Mean trough levels in CD patients were 24.8, 18.4 and 4.8 µg/ml at weeks 2, 6 and 14. Mean trough levels in UC were 19.3, 6.2 and 3.3 µg/ml at weeks 2, 6 and 14.

In the second year, we published final results of early and one-year outcomes from the prospective, nationwide cohort study on efficacy, safety and immunogenicity of biosimilar infliximab as full article in the Inflammatory Bowel Disease journal (D1,Q1). 353 consecutive inflammatory bowel disease (209 CD and 144 UC) patients were included, of which 229 patients reached the week 54

endpoint at final evaluation. Forty-nine, 53, 48% and 86, 81 and 65% of patients with CD reached clinical remission and response by weeks 14, 30, and 54, respectively. Clinical remission and response rates were 56, 41, 43% and 74, 66, 50% in patients with UC. Clinical efficacy was influenced by previous anti-tumor necrosis factor (TNF) exposure in patients with a drug holiday beyond 1 year. The mean C-reactive protein level decreased significantly in both CD and UC by week 14 and was maintained throughout the 1-year follow-up (both UC/CD: $P < 0.001$). Antidrug antibody positivity rates were significantly higher throughout patients with previous anti-TNF exposure; concomitant azathioprine prevented antidrug antibody formation in anti-TNF-naive patients with CD.

In the second study, we evaluated the predictors of loss of response in IBD patients on adalimumab therapy in 112 IBD patients included from 2 IBD centers. Among 112 IBD patients, LOR/drug persistence was 25.9%/74.1%. The cumulative ADA positivity (>10 ng/mL) and low TL (<5.0 µg/mL) was 12.1% and 17.8% after 1 year and 17.3% and 29.5% after 2 years of adalimumab therapy. Dose intensification was needed in 29.5% of the patients. Female gender and ADA positivity were associated with LOR (female gender: $p < 0.001$, OR:7.8 CI 95%: 2.5-24.3, ADA positivity: $p = 0.007$ OR:3.6 CI 95%: 1.4-9.5). Results were published in the BMC Gastroenterology Journal (Q2).

In the third year, we finalized and published the clinical and TDM outcomes in patient switching from original to biosimilar infliximab or the originator molecule in 174 unselected and consecutive patients with IBD (136 with CD and 38 with UC) who received maintenance therapy with the biosimilar in Hungary. There was no significant difference in the proportion of patients in clinical remission at week 8 before the switch (82.5% with CD and 82.9% with UC), at baseline (80.6% with CD and 81.6% with UC), at week 16 (77.5% with CD and 83.7% with UC), or at week 24 (CD 76.3% with CD and 84.9% with UC) ($P = 0.60$ among groups for patients with CD and $P = 0.98$ among groups for patients with UC). For all patients, mean serum trough levels of infliximab were 5.33 ± 4.70 µg/mL at baseline and 5.69 ± 4.94 µg/mL at week 16 ($P = 0.71$); we did not find significant differences in prevalence of anti-drug antibody at baseline (16.2%) compared with week 16 (16.9%) ($P = 0.87$). Four infusion reactions occurred, until week 24 of follow up. In conclusion, no significant changes were observed in remission, trough levels, or antidrug antibodies in patients switched from the biosimilar to Remicade. Results were published in Clin Gastroenteorl Hepatol (D1,Q1). In the extension of the follow-up, we investigated also if endoscopy remained unchanged in a subgroup of the above patients. The composite clinical and biomarker remission rates (CDAI<150/pMayo<3 and CRP<10mg/L) also remained unchanged. 22 patients had

endoscopic data during the 1-year follow up after the switch. Endoscopies were performed median 44 weeks (IQR: 19-58) after the switch, endoscopic remission rates remained unchanged following the switch (results were presented orally at the 61st Annual Meeting of the MGT).

We believe that results may have direct application to the clinical practice and suggest the selected use of early TDM in predicting initial response and later `point of care` use of TDM in predicting secondary loss of response to anti-TNF molecules. Furthermore, our study was the first to confirm that non-medical switch from biosimilar infliximab to the originator does not convey risk to the patients, thus our data confirm patient safety during a non-medical switch scenario.

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