

Formation of antiphospholipid antibodies and antibodies to infliximab in anti-TNF-alpha antibody-treated patients with inflammatory bowel diseases



Karin Malíčková¹, Ivana Janatková¹, Naděžda Machková², Dana Ďuricová², Martin Bortlík², Tomáš Zima¹, Milan Lukáš^{1,2}



¹ Institute of Clinical Biochemistry and Laboratory Diagnostics, 1st Faculty of Medicine and General University Hospital, Charles University in Prague, Czech Republic

² Clinical and Research Center for Inflammatory Bowel Disease, ISCARE a.s. and Charles University, Prague, Czech Republic

BACKGROUND

Anti-tumor necrosis factor alpha (TNF-alpha) treatment used in patients with inflammatory bowel diseases (IBD) is associated with the induction of non-organ-specific autoantibodies such as antinuclear antibodies and double-stranded DNA antibodies. The clinical relevance of these autoantibodies formation is not fully understood yet, but it is known that they can present without autoimmune clinical manifestations. Moreover, IBD are associated with an increased risk of vascular complications. The most important of these complications are arterial and venous thromboembolism, which represent a significant cause of morbidity and mortality in IBD patients.

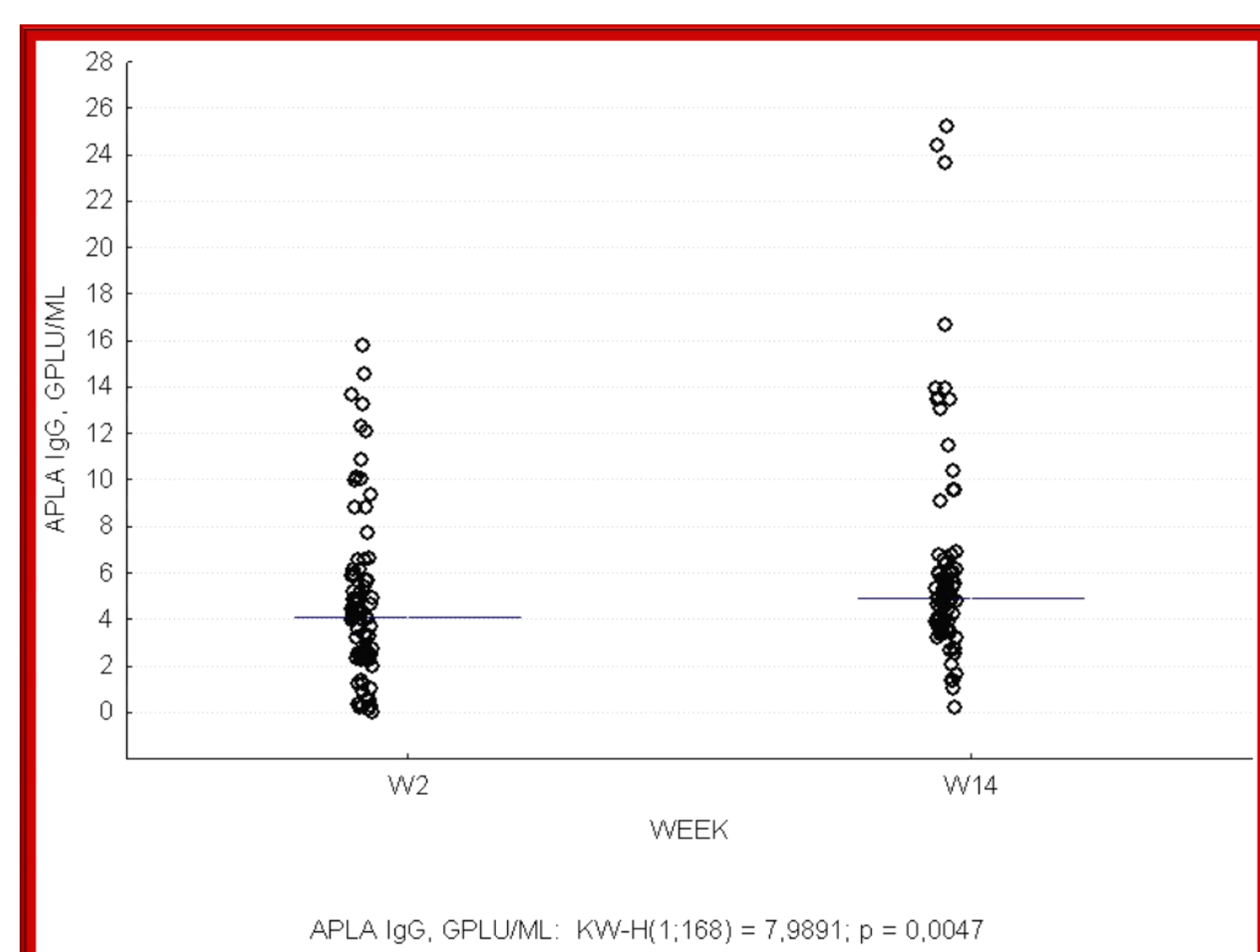
The goal of the current work was to

- examine occurrence and concentrations of antiphospholipid antibodies (APLA) in IBD patients at the beginning and during the anti-TNF-alpha therapy with infliximab;
- confrontation of APLA presence with antibodies to infliximab (ATI) formation; and
- investigate possible clinical consequences of APLA positivity in these patients.

METHODS

Eighty-five (85) IBD patients treated with infliximab were analyzed regarding APLA and ATI antibody serum levels. Median age (IQR) of patients was 33 (26;42) years, 48 (56 %) patients were males and 37 (44 %) were females, 54 (64 %) have suffered from Crohn's disease (CD) and 31 (36 %) from ulcerative colitis (UC). The treatment strategy of all patients was standardized and consisted of induction therapy with infliximab 5mg/kg at weeks 0, 2, 6 followed by maintenance regime with infliximab infusions every eight weeks.

Serum samples were taken at the beginning of induction therapy at week 2 (W2) and during the maintenance treatment at week 14 (W14). Serum APLA IgG and IgM were detected by ELISA (Anti-Phospholipid Screen IgG/IgM, Orgentec). Antibodies to infliximab (ATI) and serum infliximab levels were measured by ELISA (Q-ATI ELISA and Q-INFLIXI ELISA, respectively, Matriks Biotek).



RESULTS

At **W2**, 14/85 (17 %) of infliximab-treated patients had APLA serum levels ≥ 10 U/mL: 9 of them have shown APLA IgG, 5 have APLA IgM and none of them double IgG and IgM APLA positivity.

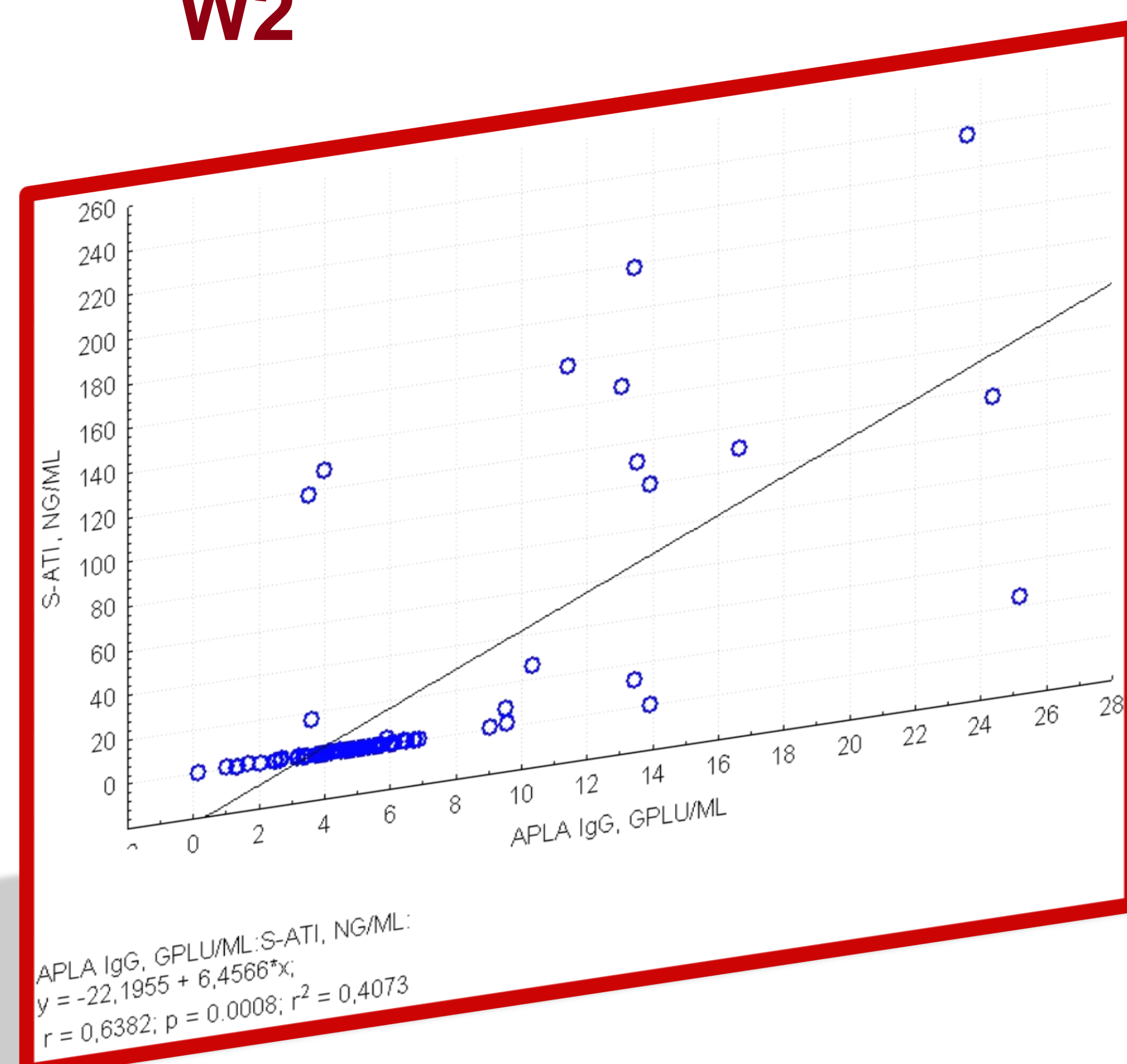
At **W14**, 12 (14 %) patients have shown elevated levels of APLA IgG and 6 (7 %) elevated APLA IgM.

With the exception of one individual with post-treatment APLA IgM of 43.50 MPLU/mL, all APLA-positive patients have only slightly elevated APLA levels ≤ 25 GPLU or MPLU/mL.

Statistical analyses did not identified age, gender or diagnosis (CD or UC) as a risk factor for developing APLA.

Concentrations of APLA IgG at W14 were significantly higher compared to W2 values ($p = 0.005$).

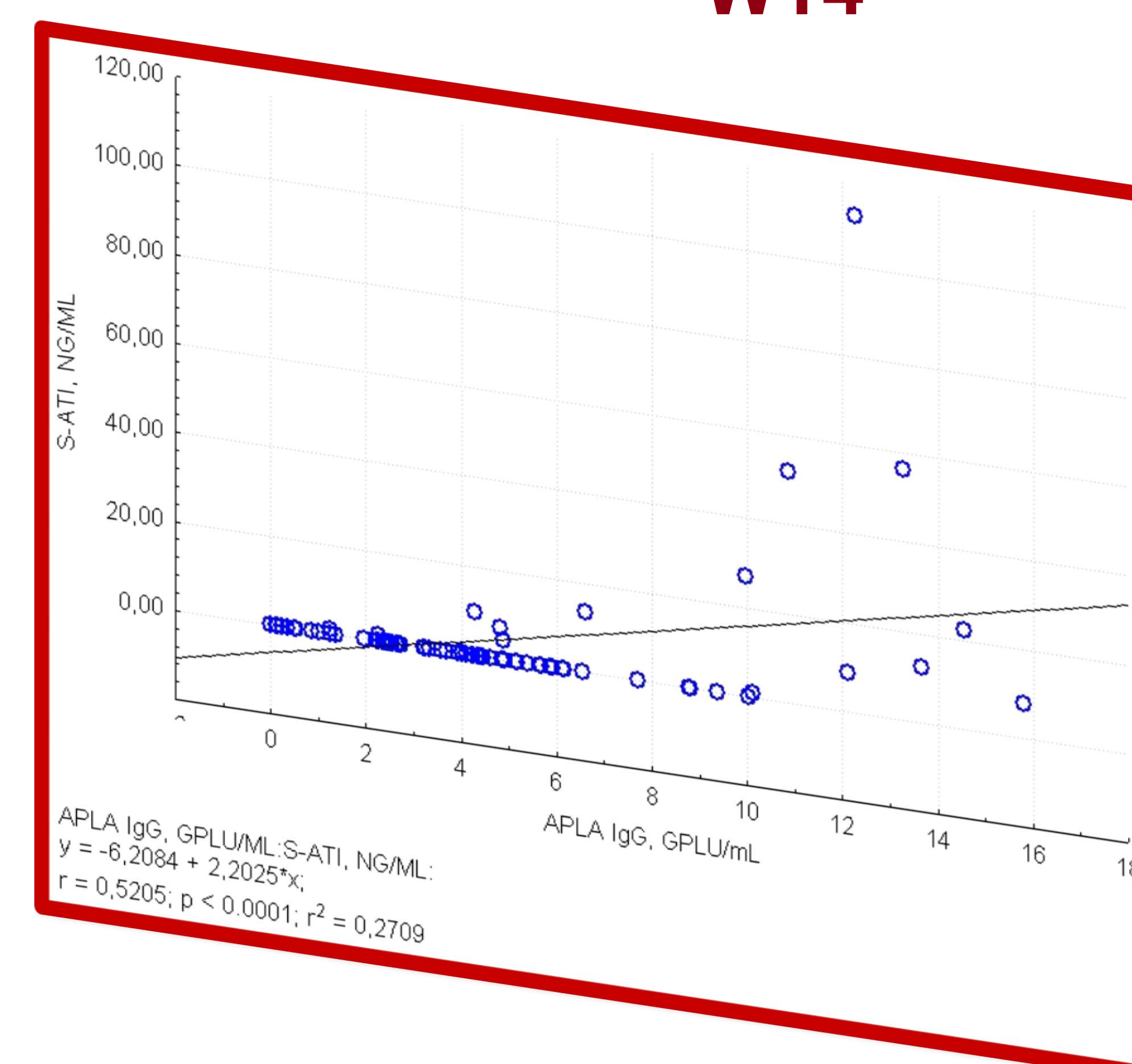
W2



For APLA IgG, occurrence of elevated levels did not depend on serum infliximab trough levels, but **strong positive correlation with ATI was found at W2 as well as at W14** ($p = 0.008$ and $p < 0.0001$, respectively).

None of APLA-positive IBD patients experienced clinical symptoms of antiphospholipid syndrome (APS) such as vascular thrombosis or recurrent miscarriages neither before neither during or after the biological treatment.

W14



CONCLUSIONS

APLA antibody levels ≤ 25 GPLU or MPLU/L in IBD patients during the biological treatment with infliximab are not associated with clinical symptoms of APS, while concomitant ATI positivity shows strong positive correlation with APLA IgG levels. Vermeire et al. speculated that antibody-dependent cell-mediated cytotoxicity of TNF-alpha producing cells by infliximab may release subcellular particles whose subsequent exposure to the immune system drives a sustained autoantibody response. Thence, it could be hypothesized that activated immune system of individuals with autoaggressive reactivity towards infliximab could be over most predisposed to phospholipid autoreactivity. However, the exact mechanisms and clinical significance of this remains to be determined.