RHEUMATOLOGY

Letter to the Editor (Case report)

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Serum sickness-like disease after switching to biosimilar infliximab

Rheumatology key message

- Serum sickness-like disease can be a complication of the switch from original to biosimilar infliximab.

SIR, a 60-year-old man was followed in our rheumatology outpatient clinic for a seronegative, non-erosive RA. The disease had begun 15 years before. He was treated with oral MTX 10 mg/week, prednisone 5 mg/day and infliximab (IFX) 5 mg/kg/8 weeks. He had received nine IFX infusions with good tolerance and efficacy. IFX was his third line of biotherapy; he had previously received etanercept and tocilizumab, which were stopped because of secondary inefficacy and an adverse effect (cytopenias), respectively. As a result of a clinical remission and an ongoing trial in the hospital, it was decided with the patient to switch from original IFX to CT-P13 (Inflectra®, Hospira France, 23-25 avenue du Docteur Lannelongue, 75014 Paris; biosimilar IFX) using the same dosage and frequency of administration.

After receiving the third infusion of Inflectra, the patient reported hyperthermia $>38.5\,^{\circ}C$ and diffuse arthralgia within 24 h following IFX infusion. These recurring episodes spontaneously abated within 2–3 days without specific treatment. Outside these episodes, the patient was asymptomatic, with no tender or swollen joint, and the CRP was low (<5 mg/l) at each visit. After reporting two similar episodes (four Inflectra infusions in total), the patient was switched back to original IFX, which resulted in the persistence of the post-infusion reaction.

The patient was then hospitalized for monitoring of the IFX post-infusion period. The night after a new infusion of original IFX (second original IFX infusion after reswitch), he presented chills, with a core body temperature of $39\,^{\circ}C$. He reported diffuse arthralgia, although no arthritis was noticed on clinical examination. The CRP concentration increased from 15 to 70 mg/l overnight. All microbiological explorations, including urine and blood cultures, thoracic X-ray, viral (CMV, EBV) PCR and hepatitis B serology, remained negative. Symptoms spontaneously abated within 2 days. Anti-drug antibodies to IFX were not measured.

The patient was diagnosed with IFX-related serum sickness-like disease (SSLD). IFX was definitively stopped, and adalimumab was introduced, with good clinical outcome and no further injection reaction. SSLD is an immune complex-mediated (type III of Gell and Coombs classification) delayed hypersensitivity reaction. Most knowledge on IFX-induced SSLD comes from gastroenterology literature, probably because of the difference in the use of IFX. Its epidemiology ranges from 0.3 to 4% of IFX-treated patients, depending on the series [1, 2].

After infusion of a foreign antigen, reaction with specific IgG antibodies induces the formation of immune complexes. This specific IgG production explains the 7–10 day time window after the first antigen infusion to SSLD onset. However, once specific antibodies are produced, repeated antigen challenge will induce SSLD within 24–48 h. Upon formation, immune complexes induce mast cell degranulation via FcγRIII, leading to liberation of pro-inflammatory cytokines. Clinical symptoms include fever, arthralgia, myalgia, cutaneous rash and dyspnoea.

Determinants of anti-drug antibody formation (and SSLD) seem to be drug holidays (*vs* continuous treatment) [3] and the absence of use of concomitant immunosuppressive therapy [3, 4]. These factors were not present in our case. The treatment of SSLD is initially, withdrawal of the culprit agent. Symptomatic treatment is used for mild SSLD, whereas systemic glucocorticoids are often used in patients with more severe systemic symptoms.

Our observation is of interest because it is, to our knowledge, the first description of SSLD after switching from original IFX to Inflectra. Even when infusion-related adverse events were described in CT-P13 core and extension studies [5, 6], no case of SSLD was reported. One of the concerns about the use of biosimilars is the risk of immunization [7]. It seems that the specific IgG involved in our patient's reaction developed (or reached clinically significant levels) after switching to biosimilar IFX. The fact that SSLD persisted after return to original IFX is not surprising because it has been shown that neutralizing antibodies to IFX cross-react between original and biosimilar products [8].

In conclusion, we report the first case of serum sickness-like disease following a switch from original IFX to Inflectra. Although the global benefit of biosimilars seems positive, continuous pharmacovigilance seems mandatory in patients being switched.

LETTER

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