

Induction of severe systemic lupus erythematosus by TNF blockade and response to an anti-IL-6 strategy: Role of IL-17?

To the Editor:

We read with great interest the article by Adler et al.¹ They reported the case of a 70-year-old retired plasterer with anterior scleritis and intraorbital and retrobulbar inflammation who had systemic lupus erythematosus (SLE) induced by TNF blocking antibody (infliximab) and a good response to anti-IL-6 therapy. They speculated that TNF inhibition could promote immunologic features of a T_H2 response, causing SLE, and that blocking the IL-6 receptor α chain with tocilizumab might inhibit systemic inflammation.¹ However, we would like to add another possible mechanism on the development of SLE after anti-TNF therapy and the beneficial effect of anti-IL-6 on that condition.

Although rare, there have been some reports showing that IL-17 levels could increase during the course of anti-TNF therapy.^{2,3} Aerts et al.² reported that T_H17 cells and IL-17 production increased after anti-TNF therapy, irrespective of disease activity, in patients with rheumatoid arthritis, and Ma et al.³ showed that neutralization of TNF- α exacerbated skin inflammation in a murine psoriasis model and markedly enhanced the expression of proinflammatory cytokines, such as IL-1 β , IL-6, IL-17, and IL-21. Recently, IL-17 has been reported to be an important cytokine in the development of SLE in human subjects and lupus-prone mice.⁴

Conversely, it was shown that IL-6 is a potent factor in switching immune responses *in vivo* from the induction of regulatory T cells to pathogenic T_H17 cells,⁵ and recent reports suggest that anti-IL-6 therapy could decrease IL-17 levels.^{5,6} Fujimoto et al.⁶ showed that when mice with collagen-induced arthritis and predominantly increased T_H17 cell frequency were treated with anti-IL-6 receptor mAb on day 0, the induction of T_H17 cells was markedly suppressed and the protective effect of IL-6 blockade was correlated with the inhibition of T_H17 differentiation. Furthermore, Aricha et al.⁵ demonstrated that administration of anti-IL-6 antibodies led to downregulation of several T_H17-related genes, including those encoding IL-17, IL-17 receptor, IL-23 receptor, and IL-21, but did not affect regulatory T-cell numbers in the lymph nodes.

Therefore, there is a possibility that SLE could be caused by an increase in IL-17 levels after anti-TNF therapy and that anti-IL-6 therapy might treat SLE through inhibition of IL-17 in addition to the blocking of IL-6 shown in the case by Adler et al.,¹ although IL-17 levels were not measured. Further studies are necessary to evaluate serial changes in IL-17 levels after anti-TNF therapy, and the exact molecular role of IL-17 in the pathogenesis in SLE development should be further elucidated.

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Reply

To the Editor:

Dr Shin¹ proposes an interesting cellular mechanism that might have played a role in our case. However, because we did not expect the development of a severe form of systemic lupus erythematosus, we did not prospectively collect data to support or dismiss her hypothesis.

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Unlocking the resistance to wheat lipid transfer protein

To the Editor:

Two cases have been published concerning wheat allergy in children with tolerance to a foodstuff of whole-grain wheat cereal biscuit (Weetabix; Weetabix Ltd, Burton Latimer, United Kingdom).¹

We present 4 patients with the lipid transfer protein (LTP) syndrome,² showing confirmed Tri a 14-mediated cereal allergy by wheat oral food challenge (OFC). These patients present multiple food allergies (tree nuts, rosaceous fruits, lettuce, and cereals). All patients had positive skin test results to wheat, nPru p 3, and nTri a 14. Sensitization to other cereal proteins (such as ω -5-gliadin and gluten proteins) was not found.

First patient: 16-year-old boy who showed urticaria, angioedema, and abdominal pain after wheat ingestion (OFC, 500 mg); specific IgE (sIgE) to rTri a 14, 66.3 KU/L; wheat, 3.89 KU/L; and rPru p 3, 320 KU/L. Second patient: 10-year-old girl with severe abdominal pain, vomiting, and urticaria after bread ingestion (OFC, 800 mg); sIgE to rTri a 14, 4.6 KU/L; wheat, 5.68 KU/L; and rPru p 3, 3.86 KU/L. Third patient: 50-year-old woman with urticaria, angioedema, and dyspnea after wheat ingestion (OFC, 200 mg); sIgE to rTri a 14, KU/L; wheat, 4.72 KU/L; and rPru p 3, 38.21 KU/L. Fourth patient: 18-year-old woman with 3 episodes of exercise-induced anaphylaxis after cereal ingestion (no OFC because of the severity of her symptoms); sIgE to rTri a 14, 1.63 KU/L; wheat, 0.35 KU/L; and rPru p 3, 310.1 KU/L.