

Restored Response to Infliximab after Treatment with Rituximab to Decrease Anti-drug Antibodies in Psoriasis

Wiggin Wu Lee, MD

Jae Jung, MD, PhD

City of Hope Comprehensive Cancer Center
University of California, San Diego

Case Presentation

59 year old male with a >20 year history of psoriasis and psoriatic arthritis presenting for evaluation and management of worsening disease

- Treatment history
 - Topical steroids under occlusion (clobetasol), PUVA, NBUVB, soriatane, MTX (many years), CSA (severe adverse reaction), etanercept, adalimumab, infliximab , ustekinumab
- Current therapy: none for last 6 months as he felt he had exhausted all treatment options
- Progressive cutaneous and joint disease

History and labs

- Past medical and surgical history
 - Testicular cancer
 - s/p orchiectomy, chemotherapy, and retroperitoneal lymph node dissection
 - Thyroid cancer
 - s/p thyroidectomy
 - Cholangiocarcinoma
 - s/p partial resection
- Family history
 - Extensive family history of psoriasis, including a severely affected brother
- Labs
 - Normal LFTs except for a slight increase AFP (followed due to history of cholangiocarcinoma)

Physical Exam

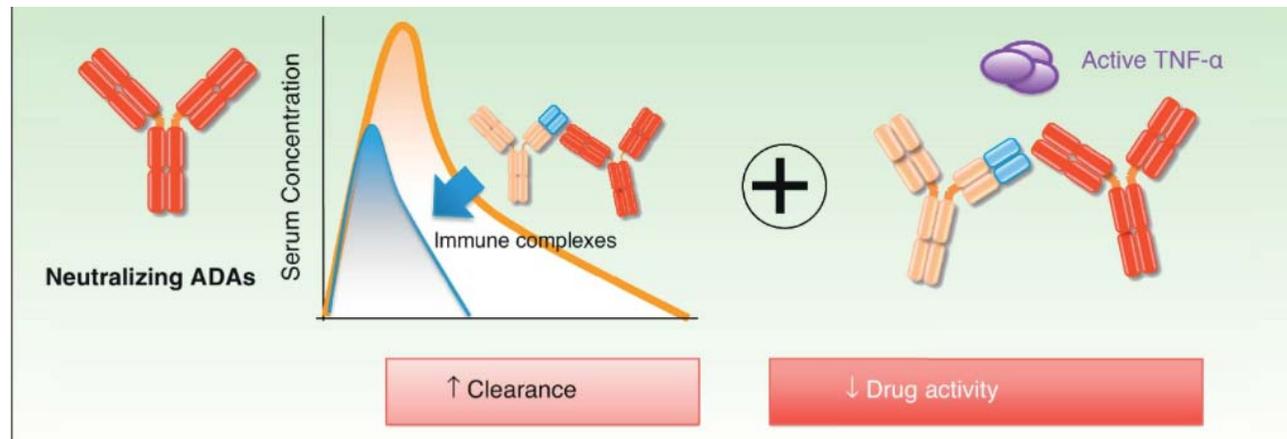


Next steps in management

- TNF inhibitor plus MTX was favored, but patient was not an ideal candidate.
 - History of cholangiocarcinoma and partial resection
 - Slightly elevated AFP 9.1 (normal 1.3-8 ng/mL)
 - Unknown total dosage of MTX
- Repeat trial of etanercept
 - No improvement after 2 months
- Repeat trial of adalimumab
 - No improvement after 2 months
- Apremilast
 - No improvement after 12 weeks
 - Worsening PSA, increasingly disabled, bilateral knee effusions, required narcotic pain medication

Anti-drug antibodies

- Postulated that TNF-inhibitor failures were secondary to neutralizing anti-drug antibodies (ADAs)
- Neutralizing ADAs may decrease the therapeutic efficacy of biologic treatments by:



Carrascosa. *Actas Dermosifiliogr.* 2013 Jul-Aug;104(6):471-9.

- Potential contributors include
 - Medication constitution
 - Mode or frequency of administration
 - Patient characteristics

Anti-drug antibodies in psoriasis

Medication	Reported rates of ADAs
Etanercept	0-18.3%
Adalimumab	5.4-43.6%
Infliximab	8.8-44.8%
Ustekinumab	3.8-5.4%

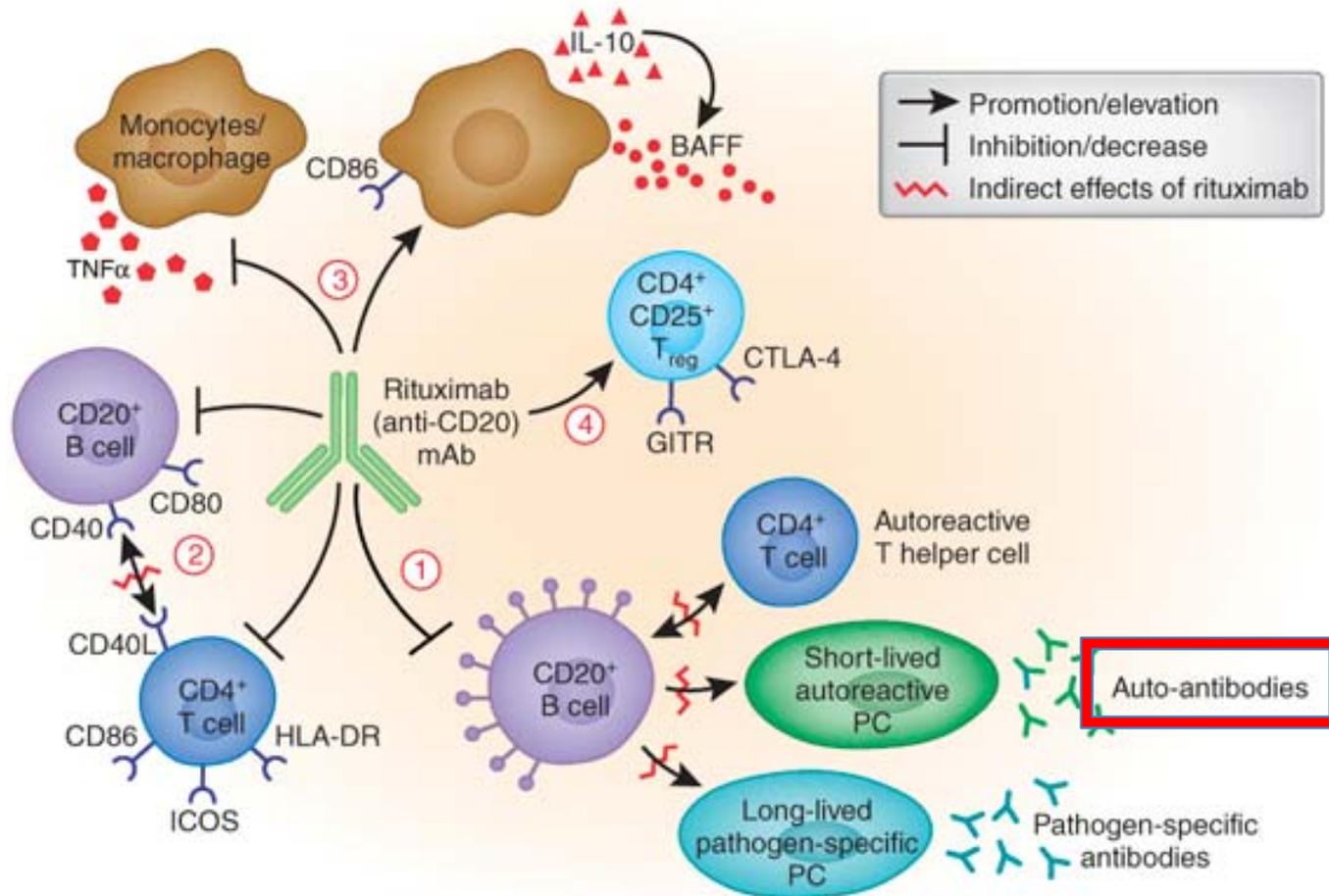
Hsu and Armstrong *Expert Rev. Clin. Immunol.* 9(10), 949–958 (2013)

- Patients with one anti-drug antibody (ADA) are more likely to develop additional ADAs

Julliens, et al. *Journal of Investigative Dermatology* (2015) 135, 31–38

- New treatment option rationale:
 - Clear neutralizing ADA and repeat trial of infliximab

Rituximab to decrease antidrug antibodies



- Rituximab administered
 - RA dosing
 - (1000 mg x2, day 1 and 15)
 - Had progression of cutaneous disease during treatment
 - Worsening joint pain with effusions
 - Partially relieved with
 - Intralesional steroid injections
 - Low dose prednisone taper
 - Narcotic pain medicine

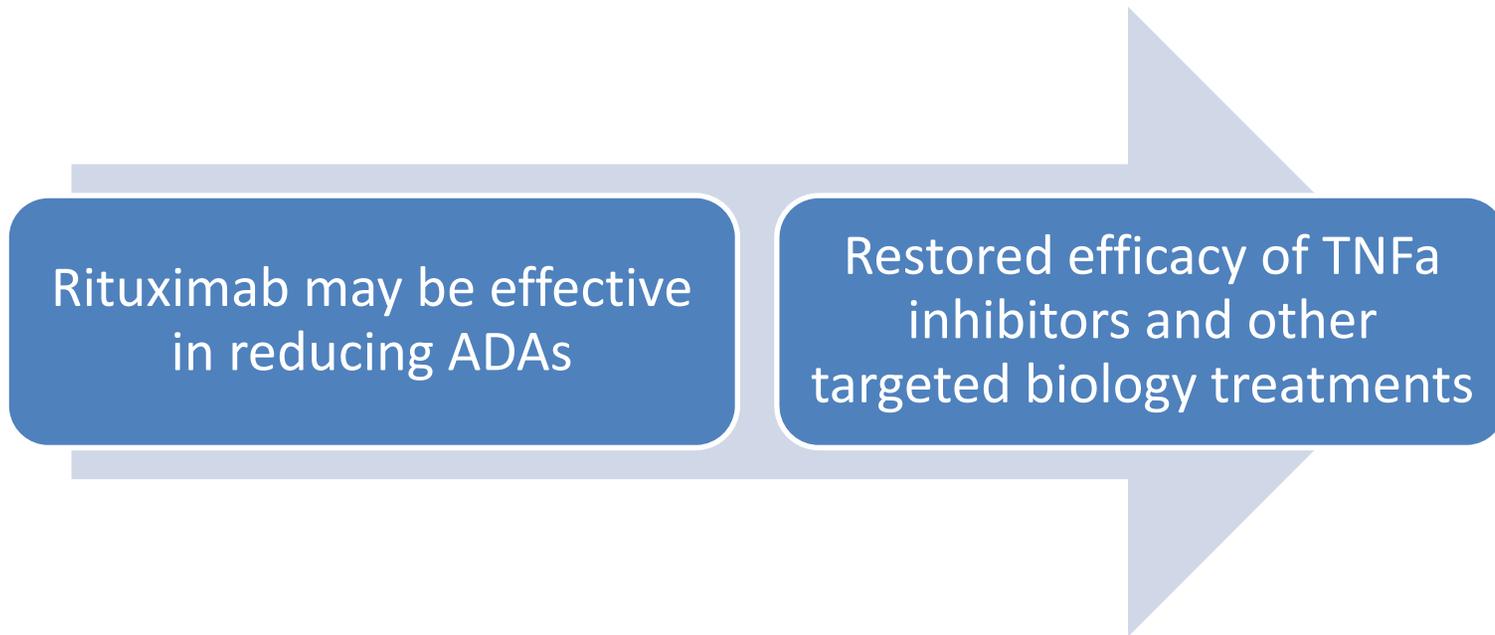


Restored response to infliximab

- Infliximab start at 5 mg/kg IV
- Rapid improvement after 1st infusion
- Virtual resolution of all lesions after 2nd infusion



Restored response to infliximab after treatment with rituximab to decrease ADAs in psoriasis



This case exemplifies the ways by which advances in basic science and immunology can guide treatment decisions and ultimately benefit patients

References

1. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet*. 2007 Jul 21;370(9583):263-71.
2. Coimbra S, Figueiredo A, Castro E, Rocha-Pereira P, Santos-Silva A. The roles of cells and cytokines in the pathogenesis of psoriasis. *Int J Dermatol*. 2012 Apr;51(4):389-95.
3. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, Gottlieb AB; Etanercept Psoriasis Study Group. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med*. 2003 Nov 20;349(21):2014-22.
4. Reich K, Nestle FO, Papp K et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet*. 2005 Oct 15-21;366(9494):1367-74.
5. Kimball AB, Papp KA, Wasfi Y et al. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis treated for up to 5 years in the PHOENIX 1 study. *J Eur Acad Dermatol Venereol*. 2013 Dec;27(12):1535-45.
6. Menter A, Tying SK, Gordon K et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled Phase III trial. *J Am Acad Dermatol*. 2008 Jan;58(1):106-15.
7. Lecluse LL, Driessen RJ, Spuls PI et al. Extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis. *Arch Dermatol*. 2010 Feb;146(2):127-32.
8. Bartelds GM, Kriekaert CL, Nurmohamed MT et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. *JAMA*. 2011 Apr 13;305(14):1460-8.
9. Ducourau E, Mulleman D, Paintaud G et al. Antibodies toward infliximab are associated with low infliximab concentration at treatment initiation and poor infliximab maintenance in rheumatic diseases. *Arthritis Res Ther*. 2011 Jun 27;13(3):R105.
10. Plasencia C, Pascual-Salcedo D, Nuño L et al. Influence of immunogenicity on the efficacy of longterm treatment of spondyloarthritis with infliximab. *Ann Rheum Dis*. 2012 Dec;71(12):1955-60.
11. Hsu L, Armstrong AW. Anti-drug antibodies in psoriasis: a critical evaluation of clinical significance and impact on treatment response. *Expert Rev Clin Immunol*. 2013 Oct;9(10):949-58.
12. Jullien D, Prinz JC, Nestle FO. Immunogenicity of biotherapy used in psoriasis: the science behind the scenes. *J Invest Dermatol*. 2015 Jan;135(1):31-8.
13. Wolbink GJ, Aarden LA, Dijkmans BA. Dealing with immunogenicity of biologicals: assessment and clinical relevance. *Curr Opin Rheumatol*. 2009 May;21(3):211-5.
14. Kriekaert CL, Bartelds GM, Lems WF, Wolbink GJ. The effect of immunomodulators on the immunogenicity of TNF-blocking therapeutic monoclonal antibodies: a review. *Arthritis Res Ther*. 2010;12(5):217.
15. Chen DY, Chen YM, Tsai WC et al. Significant associations of antidrug antibody levels with serum drug trough levels and therapeutic response of adalimumab and etanercept treatment in rheumatoid arthritis. *Ann Rheum Dis*. 2015 Mar;74(3):e16.

Thank you!