

Journal Pre-proof

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PII: S0091-6749(21)01768-1

DOI: <https://doi.org/10.1016/j.jaci.2021.11.011>

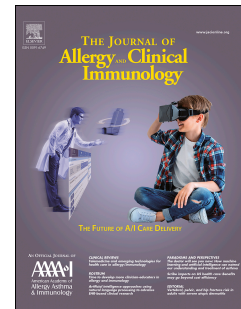
Reference: YMAI 15355

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 3 September 2021

Revised Date: 18 November 2021

Accepted Date: 18 November 2021



Please cite this article as: Dhital R, Kavanaugh A, Autoimmune Consequences of Biologics, *Journal of Allergy and Clinical Immunology* (2021), doi: <https://doi.org/10.1016/j.jaci.2021.11.011>.

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Autoimmune Consequences of Biologics

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Conflict of Interest: R.D. has nothing to declare. A.K. has consulted for AbbVie, Amgen, BMS, Eli Lilly, Janssen, Novartis, Pfizer, UCB

Key Words: biologic agents, autoimmunity, paradoxical inflammation

Recent years have witnessed tremendous progress in the therapeutic approach to autoimmune systemic inflammatory conditions. Driven by a greater understanding of the underlying dysregulated immune responses, as well as progress in biotechnology, an abundance of biologic therapies and targeted synthetic agents have been successfully brought to the clinic.(1) While this has facilitated the achievement of greatly optimized clinical outcomes for patients, there have been several unanticipated results. Some targeted therapies, failed to achieve clinical efficacy, suggesting that there may be several pathways ultimately resulting in a single disease. Moreover, some agents brought into clinical trials based on sound rationale *a priori*, worsened the disease being treated (e.g. Tumor necrosis factor inhibitors [TNFis] in multiple sclerosis, Interleukin-17 inhibitors in inflammatory bowel disease [IBD]).(2,3) Indeed, much has been learned about the immunopathology of various autoimmune diseases based on clinical trial data.(1) We may soon speak of diseases in terms of the responsiveness to targeted therapies, such as “TNF responsive IBD”. Perhaps surprisingly, other autoimmune diseases have arisen in the course of treatment of the original autoimmune diseases (e.g. psoriasis during the treatment of rheumatoid arthritis [RA] with TNFis).(4) We propose that the beneficial as well as the untoward outcomes achieved with biologic agents can be understood within the same context of involved pathways (Figure 1).

Various genetic factors modestly increase the risk of sundry autoimmune diseases. Genetic influences can be relatively disease-specific, such as HLA-Cw6 and psoriasis. Other genetic factors are associated with several autoimmune diseases that can be grouped within a family, such as HLA-B27 and the spondyloarthritis group of conditions: this includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, acute idiopathic anterior uveitis and IBD. Some genetic factors appear to be associated more broadly with propensity to diverse autoimmune diseases, such as polymorphisms in PTPN22 (protein tyrosine phosphatase non-receptor type 22 gene that affects responsiveness of T and B lymphocytes).(5) It is not clear how genetic predisposition ultimately impacts immune and inflammatory pathways or responses to therapeutics. However, we hypothesize that the association of several autoimmune diseases with single genes, such as HLA-B27 and PTPN22, may be relevant to the development of autoimmune diseases with biologic agents.

Individuals are exposed throughout their lives to a variety of influences that can impact the manner in which their immune systems will respond to exogenous and self-antigens. Environmental elements, hormonal dynamics, and the breadth and diversity of the microbiomes throughout the body can affect alterations in the proteome and metabolome that in turn influence immunocompetent cells and soluble mediators.(6) Thus, effector and regulatory cells, as well as soluble protein and lipid mediators, can provide an overall pro- or anti-inflammatory bias. Importantly, cells and mediators function in complex cascades, with individual components characterized by various levels of redundancy and pleiotropy, functioning in synergy/activation or antagonism, with other elements depending on the pathway. In health, the overall balance allows facile responses against relevant foreign and autologous challenges, with tolerance to, or ignorance of appropriate antigens. Alteration in the fine balance of stimulatory and inhibitory pathways leads to autologous immune activation and autoimmune diseases.

Biologic agents target specific, key components of the dysregulated immune response.(1) Given the complex cascades in the inflammatory and immune responses, it is perhaps surprising that therapy inhibiting a single target, for example TNF, is effective in many complex autoimmune diseases. Such impressive clinical responses have been achieved that the goals and approaches to therapy have been rewritten for autoimmune diseases. The success achieved initially with TNF inhibitors has spawned further research and discovery, and there are now dozens of highly effective biologic agents for diverse autoimmune diseases. Interestingly, while some patients do achieve remission of their autoimmune disease with biologic therapy, not all patients with a given condition respond to modulation of the same pathway. Currently, there are limited data identifying factors to inform selection of a specific biologic therapy for an individual with a particular autoimmune disease. Thus, the ideal of “personalized medicine” or “the right medicine for the right patient” remains elusive.

Some of the adverse events associated with biologic agents may be considered target-related, insofar as they can be understood based on the mechanism of action of the treating agent, most of which modulate components of the immune and inflammatory responses.(7) Not uncommonly, patients experience an increased incidence of infections, sometimes opportunistic infections, as a result of treatment. Interestingly, this target-related mechanism may underlie some apparent autoimmune consequences of biologic agents. For example, inhibitors of Interleukin-17 had great promise as potential therapies for IBDs, given the key role of that inflammatory cytokine in those diseases. However, not only was this therapy ineffective, it was associated with flares of IBD.(3) The underlying explanation may relate to alterations in gut epithelial integrity and the fungal microbiome resultant from Interleukin-17 inhibition, which has a role in bowel homeostasis and gut inflammation. IL-17 plays a central role in, and its inhibition has been clinically effective for, other conditions such as psoriasis, PsA and AS; this relates presumably to its ability to upregulate IL-23. In another example, demyelinating central nervous system (CNS) diseases, including neuromyelitis optica and multiple sclerosis, have been associated with TNFi use, possibly secondary to interference with TNF receptor 2-mediated signaling in the CNS, which has a role in remyelination.(2)

One of the earliest autoimmune consequences noted with biologic therapy was the development of new autoantibodies in RA patients treated with TNFis. Several mechanisms have been proposed to explain TNFi-induced autoantibodies.(8) TNFis can promote humoral immunity by inhibiting cytotoxic T lymphocyte response, which ordinarily suppresses autoreactive B-cells. TNFis can also bind to the transmembrane form of TNF- α , inducing antibody- or complement-dependent cytotoxicity of the cells expressing TNF on their surface with release of autoantigens. The extracellular autoantigens may stimulate autoreactive B-cells to produce autoantibodies.(8) TNFis can alter TH1/TH2 balance, suppressing TH1 cytokine production and shifting the immune response towards TH2 cells, and increasing interferon- α , which can be involved in the pathogenesis of systemic lupus erythematosus (SLE) and other autoimmune conditions. The most common autoantibodies induced include antinuclear antibodies (ANAs) and anti-double-stranded DNA (dsDNA) antibodies, but an association with anti-phospholipid (aPL) antibodies has also been reported. Interestingly, despite the induction of autoantibodies by TNFis, clinical manifestations of SLE or vasculitis are rare, highlighting that the role of autoantibodies may be necessary but not sufficient, and that other factors are necessary for the expression of autoimmune diseases.(8)

Another autoimmune consequence of biologic therapy is the induction of skin psoriasis among patients with other autoimmune diseases (RA, IBD, AS) on TNFi therapy.(4) In registries, this is the most common autoimmune disease arising from biologic therapy, with prevalences from 0.6% to 5 % of treated patients. It was considered a curiosity initially, as TNFis are generally highly effective therapies for skin psoriasis. The pathogenesis of TNFi-induced psoriasis is not entirely understood but, the disruption of the cytokine balance is thought to be the key, with TNF blockade allowing for unopposed interferon- α production by plasmacytoid dendritic cells (pDCs).(9) pDCs are key interferon producing cells. TNF- α downregulates interferon- α production by inhibiting pDC maturation from hematopoietic progenitors and also inhibiting IFN- α release by activated pDCs.(9) Biopsies of TNFi induced psoriatic lesions show increased interferon- α activity in the dermal vasculature and perivascular inflammatory infiltrate.(4) Increased IFN- α -activity can result in abnormal trafficking of pDCs to the skin. IFN- α can also induce the expression of CXCR3 on T-cells, promoting T-cell migration to the dermis and subsequent homing to the epidermis.(4)

Other autoimmune consequences of biologic therapy may represent an incomplete control of the treated disease and subsequent emergence of other signs and symptoms. For example, uveitis occurs more commonly with the soluble receptor construct TNFi etanercept as compared to monoclonal antibodies specific for TNF- α in the treatment of AS patients; this may represent lesser efficacy for specific manifestations of the autoimmune diseases, perhaps via a dose effect.(10) Similarly, flares of arthritis

have been reported with the anti-integrin vedolizumab therapy of IBD patients. This may represent less control of the diverse aspects of IBD, allowing the emergence of IBD-related arthritis.

In conclusion, biologic therapies, that alter key components of the immune response, have not only allowed significant improvement for many patients with autoimmune conditions, they have also helped us define the relevant immunologic and inflammatory pathways germane to individual patients. Moreover, biologic agents can themselves result in immune imbalance. Adverse events associated with such perturbation can include the development of autoimmune diseases. A greater understanding of these concepts will aid in the proper application of these agents and improved patient outcomes.

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Figure legends:

Figure 1. Proposed basis for variable outcomes of systemic inflammatory autoimmune diseases to targeted biologic therapies. Some patients, with genetic predisposition are exposed to various factors that can effect alterations to their immune and inflammatory pathway responses, ultimately resulting in clinical autoimmune diseases. As a result of targeted therapies, key pathways are inhibited. Possible outcomes include clinical response to varying extents (including non-response), adverse effects (AEs) related to mechanism and expression of other autoimmune diseases. The latter may relate to alteration in specific disease related pathways, or to incomplete control of all domains of a given clinical condition

Multiple Sclerosis (MS)
Inflammatory Bowel Disease (IBD)
Systemic Lupus Erythematosus (SLE)
Psoriasis (PsO)
Psoriatic arthritis (PsA)
Uveitis
Rheumatoid arthritis (RA)

Table 1: List of autoimmune diseases discussed in the review

