Editorial

On Anti-Tumor Necrosis Factor-induced Systemic Lupus Erythematosus

In the 1950s and 1960s Geritol tonic was heavily advertised on television as a fast cure-all if “you’re feeling weak and rundown, tired or nervous.” It was lampooned in a more recent sitcom as a magic elixir capable of transforming a friendless geek into the most popular kid at school. While the recent and numerous television advertisements for the anti-tumor necrosis factor (TNF) agents currently on the market do not make such outlandish claims as this, one cannot help but be awed by the overwhelming presence that these intravenously infused prescription drugs have so quickly established in the public sphere.

TNF-α generates a vast array of biological properties, including cellular differentiation, proliferation, and apoptosis. This variability is attributed to the binding of TNF to 2 distinct transmembrane receptors that can mediate TNF-induced inflammation and cell death, the promotion of proliferative responses in T lymphocytes and other hematopoietic cells, and the induction of apoptosis in mature activated T cells. Thus, TNF can serve dually as a potent proinflammatory mediator and a key immune modulator.

Due to the multifarious effects of TNF, the results of either TNF administration or blockade have varied significantly from disease to disease and from animal models to human patients. In terms of TNF blockade, currently 3 anti-TNF agents are licensed for clinical use (the 2 monoclonal antibodies adalimumab and infliximab and a soluble TNF receptor, etanercept) and are prescribed for the treatment of rheumatoid arthritis (RA), juvenile RA, psoriatic arthritis, chronic inflammatory bowel disease (IBD), and ankylosing spondylitis.

Contrasting the beneficial effects of TNF neutralization, TNF administration in animal models of spontaneous insulin-dependent diabetes mellitus reduces the incidence of the disease. Similarly, models of systemic lupus erythematosus (SLE) have clearly demonstrated the beneficial effects of early administration of recombinant TNF or TNF-inducing agents on inhibition of lupus nephritis. Indeed, autoimmunity and nephritis are accelerated in lupus-prone mice deficient in TNF.

Taken together, these disparate findings suggest that the clinically relevant pathophysiological role for TNF in certain disorders is that of a proinflammatory agent. Hence, neutralization or elimination of TNF is beneficial. In other disorders, however, the role for TNF as an immune regulator seems to be more important clinically, therefore administration or induction of TNF is ameliorative (while its blockade may be detrimental).

Accordingly, the complexity of the divergent effects of TNF is further exemplified by reports that, rather than improving their condition, use of anti-TNF in patients with multiple sclerosis has resulted in immune activation and disease exacerbation. Moreover, anti-TNF treatments in some patients with RA or chronic IBD incite the development of autoantibodies, neuroinflammatory disease, or SLE-like features. Nevertheless, it has been suggested that anti-TNF agents can be therapeutically administered to SLE patients, emphasizing the pressing need for a greater understanding of the multiple (and often divergent) roles of TNF in various conditions.

The current report by Soforo, et al in this issue of The Journal presents 6 patients who, during anti-TNF therapy, developed active SLE, fulfilling 4 or more American College of Rheumatology criteria for diagnosis. Although lupus-like symptoms are not uncommon after TNF blockade, these cases are unique in that they are associated with major organ involvement and life-threatening manifestations. It might be difficult to argue against the possibility that some of these subjects had underlying predisposition to SLE (or undiagnosed mild SLE), and therefore, these cases represent exacerbation of SLE under anti-TNF treatment rather than induction of de novo SLE. The major point of Soforo, et al’s observations, however, is that TNF blockade for SLE may be inappropriate, a view that we support regardless of whether or not these individuals represent

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genuine de novo cases of SLE, or are cases of underlying predisposition to SLE (or undiagnosed mild SLE) exacer-
bated by anti-TNF. The induction of SLE following TNF
blockade reported in this study is further highlighted by the
recent results of Jacob, et al. in the lupus-prone NZM 2328
mouse model, which show that abrogating the effects of
TNF by deleting both TNF receptors leads to a heightened
and distinct inflammatory pathway that accelerates onset of
disease, supporting the notion that anti-TNF may be con-
traindicated in the treatment of SLE.

Another consideration regarding these case reports is
whether they represent the latest class of drug-induced
lupus; or rather, represent a distinct syndrome of
“anti-TNF–induced lupus.” We believe that the term
drug-induced SLE should remain associated with the classi-
cal presentation due to procainamide, which has a milder
disease course than classical SLE, and in which anti-dsDNA
antibodies generally do not develop. We tend to agree with
Williams, et al. that anti-TNF–induced SLE is quite distinc-
t from classical drug-induced lupus in that it seems to be
associated with a more severe disease presentation that
includes cutaneous, renal, and central nervous system
involvement and anti-dsDNA antibodies, and that necessi-
tates additional treatment beyond cessation of the anti-TNF
regimen. In the cases presented by Soforo, et al., discontinu-
ation of anti-TNF agents alone was insufficient, supporting
their classification as anti-TNF–induced SLE, rather than
drug-induced lupus.

The significant increase in the occurrence of antinuclear
antibody and anti-dsDNA antibodies with anti-TNF treat-
ment is well documented. However, the incidence of SLE
with the use of TNF blockade is very low and the incidence
of anti-dsDNA antibodies in such patients does not predict
the development of full-blown SLE. Given the important
immunoregulatory effects of TNF, the breakdown of which
presumably can result in adverse disease manifestations,
why are there not more cases/reports of systemic autoim-
unity resulting from this loss of TNF-induced immune
regulation? Moreover, how are we to explain some of the
anecdotal reports of the benefit following anti-TNF treat-
ment in a few patients with SLE?

One potential answer is that the current anti-TNF agents
provide an incomplete blockade of TNF. That is, there is still
free TNF available to provide certain protective effects.
Thus, some proinflammatory effects of TNF are mitigated
while some of the immunoregulatory functions remain
intact. A non-mutually exclusive possibility is that most
patients treated so far who have benefited from anti-TNF are
Caucasians possessing HLA class II genotype of DR3
and/or DR4, who have been shown to be capable of produc-
ing higher levels of TNF in response to activation.
Consequently, reducing TNF levels in such patients might
mitigate the inflammatory response while preserving suffi-
cient TNF levels to provide protective regulation. Thus, this
could explain the low frequency of development of systemic
autoimmunity in patients treated with anti-TNF agents. Four
out of 6 patients presented by Soforo, et al. are Caucasians
who still developed these manifestations, but we do not
know their HLA class II genotype or their TNF inducibility.
However, the fact that they are Caucasian and might have
DR3 or DR4 genotype, and concomitant high TNF
inducibility, and still develop this adverse effect underscores
the caution that must be applied with these agents.

One should also keep in mind that DR2/DQw1-positive
subjects (mostly non-Caucasian) have lower TNF inducibil-
itv, and therefore might be more prone to the harmful con-
sequences of TNF blockade. Thus, for this population of
patients even more circumspection is suggested before using
TNF antagonists.

There is no question that anti-TNF agents have improved
the lives of many individuals suffering from RA and are
beneficial in other conditions as well. With this benefit in
mind, however, TNF antagonists should not be viewed as
wonder tonics or magical elixirs capable of curing all
rheumatologic conditions.

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REFERENCES

1. Goeddel DV, Aggarwal BB, Gray PW, Leung DW, Nedwin GE,
Palladino MA, et al. Tumor necrosis factors: gene structure and
biological activities. Cold Spring Harb Symp Quant Biol
2. Beutler B, Cerami A. Tumor necrosis, cachexia, shock, and
inflammation: a common mediator. Annu Rev Biochem
3. Sugarman BJ, Aggarwal BB, Hass PE, Figari IS, Palladino MA,
Shepard HM. Recombinant human tumor necrosis factor-alpha:
effects on proliferation of normal and transformed cells in vitro.
4. Kollia G, Kontoyianni D. Role of TNF/TNFR in autoimmunity:
specific TNF receptor blockade may be advantageous to anti-TNF
5. Tartaglia LA, Weber RF, Figari IS, Reynolds C, Palladino MA,
Goeddel DV. The two different receptors for tumor necrosis factor
mediate distinct cellular responses. Proc Natl Acad Sci USA
6. Baud V, Karin M. Signal transduction by tumor necrosis factor and
7. Tartaglia LA, Goeddel DV, Reynolds C, Figari IS, Weber RF,
Fendly BM, et al. Stimulation of human T-cell proliferation by
specific activation of the 75-kDa tumor necrosis factor receptor.
Induction of apoptosis in mature T cells by tumor necrosis factor.


J Rheumatol 2010;37:3–5; doi:10.3899/jrheum.091071