Anti-tumor necrosis factor therapy and influenza: keeping it in perspective

Matt Shale, Markus Czub, Gilaad G. Kaplan, Remo Panaccione and Subrata Ghosh

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Abstract: The association of opportunistic infections in the context of anti-tumor necrosis factor (TNF) antibody therapies have attracted widespread attention. The recent H1N1 influenza pandemic brought this into sharp focus with numerous patient queries and physician anxieties. The following short review gives a scientific perspective to this issue including the role of vaccination.

Keywords: influenza, vaccine, anti-tumor necrosis factor antibody, inflammatory bowel disease

Introduction

In the last decade, biological therapies targeting tumor necrosis factor- α (TNF- α) have played an increasingly important role in the management of inflammatory conditions, including rheumatoid arthritis, spondyloarthropathies, psoriasis, and the inflammatory bowel diseases (IBDs) Crohn's disease and ulcerative colitis [Deighton *et al.* 2006; Hanauer *et al.* 2006; Smith *et al.* 2005]. There is a clear benefit in all of these immune-mediated therapies of anti-TNF therapy in both the short term and the long term, but this must be balanced against the risks associated with the use of such potent agents, and in this regard particular attention has been paid to the risk of infection, including with opportunistic organisms [Winthrop, 2006]. Specific risks with the use of anti-TNF therapy have been reported to include reactivation of tuberculosis [Keane *et al.* 2001], *Pneumocystis jirovecii* [Komano *et al.* 2009], invasive fungal infections [Lee *et al.* 2002] and herpes zoster [Strangfeld *et al.* 2009]. Interest has recently been focused on the appropriate use of vaccination to minimize infection risk in patients receiving anti-TNF therapy, resulting in consensus statements from gastroenterology [Rahier *et al.* 2009], rheumatology [Deighton *et al.* 2009] and dermatology expert groups [Lebwohl *et al.* 2008]. Although subtle differences exist between the recommendations made in these statements, a consistent observation is the relative paucity of evidence regarding the effect of immunomodulator (purine antineoplastic and methotrexate) or biological therapy on the risk of common, potentially preventable

infections, such as pneumococcal disease or influenza. The practice of widespread immunizations against some of these common organisms in the context of anti-TNF therapy or immunosuppressive therapy is still evolving. Whilst these therapies undeniably impair aspects of the immune response, the specific risk profile of each class of drug remains largely unknown. The current pandemic of swine-derived H1N1 influenza [Centres for Disease Control, 2009] has highlighted this lack of data, and focused interest regarding the potential influence of anti-TNF therapy on susceptibility to influenza infection and the severity of subsequent disease.

TNF and influenza

Immunological events in acute influenza infection are complex, and involve the interplay of humoral and cell-mediated immunity. The role of TNF- α in this interplay is not well understood. Levels of TNF- α have been shown to correlate with symptoms in human influenza [Fritz *et al.* 1999], and with the extent of fever and lung disease in porcine models [Kim *et al.* 2009]. Viral replication within lung epithelial cells is strongly inhibited by TNF- α [Seo and Webster, 2002], and the virulence of H5N1 avian influenza may be partly related to its resistance to host TNF- α [Seo *et al.* 2002]. However TNF^{-/-} mice demonstrate similar morbidity and mortality to wild-type animals when infected with H5N1 [Salomon *et al.* 2007]. Indeed, TNF- α has been implicated in the lung immunopathology associated with severe influenza, leading to suggestions that anti-TNF treatment might actually be

Correspondence to:

Subrata Ghosh

Head of Division of
Gastroenterology,
Professor of Medicine,
Division of
Gastroenterology, TRW
Centre, 3280 Hospital
Drive NW, Calgary, AB,
Canada T2N 4Z6
ghosh@ucalgary.ca

Matt Shale

Gastrointestinal Section,
Imperial College London,
Hammersmith Hospital,
Du Cane Road, London
W12 0NN, United Kingdom

Markus Czub

Virology and Emerging
Infectious Diseases
Faculty of Medicine
University of Calgary
3330 Hospital Drive
NW Calgary, AB, Canada
T2N 4N1

Gilaad G. Kaplan
Remo Panaccione

Division of
Gastroenterology,
Department of Medicine,
Faculty of Medicine,
University of Calgary,
TRW Centre, 3280 Hospital
Drive NW, Calgary,
AB, Canada T2N 4Z6

beneficial [Hussell *et al.* 2001]. With these disparate lines of evidence predicting the consequences of anti-TNF treatment on the risk or course of influenza is therefore difficult.

Risk of influenza in anti-TNF treated patients

Current expert opinion is that patients on immunosuppression or biological therapy are at increased risk from influenza, although no data exists to confirm this [Deighton *et al.* 2009; Rahier *et al.* 2009; Lebwohl *et al.* 2008; Fiore *et al.* 2007]. Analysis of US Food and Drug Administration (FDA) pharmacovigilance data reveals 714 cases of influenza (541 females, 163 males, median age 57, range 9–87) reported in association with anti-TNF therapy in the 5-year period ending in 2008, including 7 deaths [FDA, 2009]. Etanercept (Enbrel, Wyeth) was the most frequently implicated drug, in 345 cases, followed by adalimumab (Humira, Abbott) in 305 cases, infliximab (Remicade, Schering-Plough) in 60 cases, and a combination of drugs in 4 cases, probably reflecting usage volumes. Interpretation of such data must be done with caution, and recognize the inherent limitations of the spontaneous reporting by which these cases are collected. The differences in absolute numbers may reflect simply extent of usage of these anti-TNF agents in the different immune mediated diseases, with

the absolute denominators unknown. Patients were receiving treatment for rheumatoid arthritis, spondyloarthropathies, IBD and psoriasis. Approximately 40% of patients were receiving treatment with concomitant immunomodulators, corticosteroids or both (Table 1). In particular, differences in case numbers between different drugs may reflect confounding by the underlying indication, with rheumatoid arthritis patients at increased risk of infection even in the absence of immunosuppression [Doran *et al.* 2002]. Similarly, data reporting whether influenza vaccination had been undertaken is not available. Underreporting of events to such datasets may mask their true frequency; however, in view of the novelty of anti-TNF drugs and heightened interest in their safety, severe infective events might be less likely to be ignored and not reported. Overall, postmarketing experience appears relatively reassuring both that anti-TNF treated patients may not be at any specifically increased risk of influenza and that severe adverse outcomes, including death, do not appear to be unusually frequent.

H1N1 influenza and anti-TNF therapy

The specific interaction of anti-TNF therapy and the current H1N1 virus is unknown, with no

Table 1. Influenza associated with anti-tumor necrosis factor therapy reported to the US Food and Drug Administration 2004–2008.

		IBD	Psoriasis/Psoriatic arthropathy	Rheumatoid arthritis	Spondyloarthropathy	Other indication
		<i>n</i> = 60	<i>n</i> = 162	<i>n</i> = 407	<i>n</i> = 31	<i>n</i> = 54
Etanercept (<i>n</i> = 345)	Monotherapy		116	108	17	15
	+IM*	—	9	61	6	7
	+CS	—	—	2	—	—
	+IM + CS	—	—	4	—	—
Adalimumab (<i>n</i> = 305)	Monotherapy	30	28	79	5	21
	+IM*	5	1	46	1	5
	+CS	6	2	34	—	—
	+IM + CS	1	—	41	—	—
Infliximab (<i>n</i> = 60)	Monotherapy	10	4	6	1	3
	+IM*	1	1	5	1	1
	+CS	3	—	7	—	—
	+IM + CS	4	—	11	—	2
Combined anti-TNF (<i>n</i> = 4)	Monotherapy	—	—	1	—	—
	+IM*	—	1	1	—	—
	+CS	—	—	1	—	—
	+IM + CS	—	—	—	—	—

TNF, tumor necrosis factor; IBD, inflammatory bowel disease; IM, immunomodulators; CS, corticosteroids. Immunomodulators include methotrexate, azathioprine, 6-mercaptopurine, leflunomide.
*Immunomodulator was methotrexate in 80% of cases.

reported cases of infection occurring in patients receiving such treatment. However, patterns of disease in other groups suggest that few significant differences from 'seasonal' influenza should exist, with the majority of deaths and severe complications having occurred in those groups that would be predicted to experience adverse outcomes: those with co-morbid conditions, particularly respiratory disease, diabetes mellitus, the obese and women in late pregnancy. Pregnancy presents an increased risk for influenza-associated illness and death. While in pregnant women the increased risk is believed to be associated with changes in the immune and hormonal systems, spontaneous pregnancy loss, fetal death and preterm delivery appear to be related to influenza-induced hyperthermia. In the classical model of pathogenesis, induction of fever is mediated by the release of pyrogenic cytokines such as TNF- α , interleukin-1 (IL-1), IL-6 and interferons [Rasmussen *et al.* 2008]. A notable observation is the relative sparing of older patients by the current pandemic, possibly due to residual immunity from previous exposure to related influenza strains [Centres for Disease Control, 2009]. However, with IBD being the disease of young people, this would remain a vulnerable age group for H1N1 virus.

Recommendations

A number of advisory statements have now been issued specifically regarding swine flu in patients receiving immunosuppression and biological therapy. The British Society of Rheumatology recommends stopping all immunosuppressive and biological therapy for 7 days where exposure to confirmed swine flu occurs, and the use of antiviral drugs combined with cessation of therapy until all symptoms have resolved in the case of suspected infection [British Society for Rheumatology, 2009]. Similar guidance is given by the Australian Rheumatology Association [ARA, 2009]. The UK National Association for Colitis and Crohn's Disease (NACC) does not go so far, suggesting consideration of antiviral therapy where patients have close exposure to a case of swine flu, and consideration of delaying dosing with anti-TNF where symptoms occur, but does not specifically discuss cessation of other therapies [NACC, 2009]. The UK Health Protection Agency advocates antiviral prophylaxis in immunosuppressed patients in close contact with swine flu [Health Protection Agency, 2009].

The potential of anti-TNF therapy to mask typical features of infection such as fever is not clear, but a low threshold should be employed in considering the diagnosis.

As with annual influenza vaccination, patients receiving iatrogenic immunosuppression are recommended recipients of H1N1 vaccination. A number of studies have addressed the effect of anti-TNF therapy on the response to annual trivalent inactivated influenza immunization, and show that it is both safe and effective in patients receiving etanercept, adalimumab or infliximab [Lu *et al.* 2009; Gelinck *et al.* 2008; Kaine *et al.* 2007; Kapetanovic *et al.* 2007; Fomin *et al.* 2006]. Although anti-TNF therapy may impair resulting mean antibody titres following vaccination, levels adequate to provide protection are achieved in a similar proportion of patients as healthy controls. Concomitant immunosuppression does not appear to alter this protection. A more limiting factor in protecting patients comes from the consistently low rates of uptake of influenza immunization reported in cross-sectional studies of such patients [Melmed *et al.* 2006; Bridges *et al.* 2003]. This is also observed in IBD patients [Melmed, 2009]. In influenza vaccine studies there are contradictory reports of immunogenicity of influenza vaccination in IBD/rheumatoid arthritis patients receiving biologics [Melmed, 2009]. Mamula *et al.* studied 51 paediatric IBD patients and 29 healthy controls administered single-dose inactive trivalent influenza vaccine. The patients were on combination infliximab and immunomodulatory drugs, immunomodulatory drugs alone or anti-inflammatory drugs. Overall seroconversion rates to influenza vaccine ranged from 33% to 85%, but patients on combination infliximab and immunomodulatory drugs were identified as being at risk of inadequate response to influenza vaccine [Mamula *et al.* 2007]. The vaccine appears to be safe in IBD patients and adverse effects were minor. The ideal time to vaccinate may be prior to introduction of any immunosuppressant agents. However, given the short-term protection offered by influenza vaccination, including H1N1 vaccine, and the seasonal nature of the risk, this may prove impractical.

The use of antiviral medications appears safe in patients with inflammatory conditions, with no reports of specific adverse effects relevant to those conditions for which anti-TNF therapy is indicated. Similarly, antiviral drugs appear to

be safe to use alongside immunomodulator drugs. Whilst a potential interaction between oseltamivir (Tamiflu, Roche) and methotrexate has been noted, resulting in increased methotrexate levels, this is unlikely to be of clinical significance at the doses employed in treatment of inflammatory diseases [National Electronic Library for Medicines, 2009].

H1N1 vaccination is in addition to standard vaccination for influenza. Thus, IBD patients may be requiring two vaccination doses in the autumn. This may impair compliance and it raises the issue of the risk of vaccinations triggering flares; however, the evidence does not support this in other diseases such as rheumatoid arthritis and multiple sclerosis. It may be best to avoid the nasal spray FluMist live H1N1 vaccine in those with a weakened immune system such as IBD patients on steroids, immunomodulatory drugs or anti-TNF drugs [Melmed, 2009]. While safety of trivalent inactivated influenza vaccine in IBD patients have been reported by several groups, live vaccination should be avoided as a general recommendation in immunocompromised patients.

Conclusion

Overall, the risk of H1N1 influenza in patients receiving anti-TNF therapy appears similar to that of the background population, with at most a modest theoretical increase in risk of infection or developing severe disease. However, there is little firm evidence to allow accurate assessment, and it would seem prudent to consider such patients to be at potentially increased risk when determining strategies of the use of antiviral therapy or immunization [Viget *et al.* 2008]. The current pandemic represents a significant opportunity to further define the safety of anti-TNF agents with regard to influenza through assessment of rates of clinical and serological evidence of infection. Such evidence may prove to be of future importance in the event of pandemic influenza with a more virulent strain, such as H5N1. Overall, the initial experience of H1N1 influenza in anti-TNF treated patients has been relatively reassuring but continued vigilance is necessary. A recent publication stresses that pragmatic advice in the absence of robust evidence is all that may be offered, including pneumococcal vaccine in addition to influenza and H1N1 vaccine to prevent concurrent bacterial infections [Rahier *et al.* 2010].

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