Autoimmunity Reviews 13 (2014) 54–58

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Demyelination and other neurological adverse events after anti-TNF therapy

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ARTICLE INFO

Article history:
Received 20 August 2013
Accepted 29 August 2013
Available online 12 September 2013

Keywords:
TNFα antagonists
Neurological adverse events
Multiple sclerosis
tmTNFα
sTNFα
TNFR1,2

ABSTRACT

Tumor necrosis factor (TNF) α inhibitors are an essential therapeutic option for several inflammatory diseases, like rheumatoid arthritis, spondyloarthropathies and inflammatory bowel diseases. As TNFα antagonists have become increasingly utilized, there have been a number of reports of neurological adverse events in patients receiving anti-TNFα therapy. The frequency of central nervous system adverse events after initiation of anti-TNFα therapy is unknown. However, questions have been raised about a possible causal association. Although several hypotheses have been proposed in an attempt to explain the possible relationship between TNFα antagonist and demyelination, none is considered to be adequate. Thus, in this report we deal with the implication of TNFα in multiple sclerosis and we discuss the possible relationship of TNFα antagonist and demyelinating diseases.

Contents

1. Introduction

The discovery of biologics and the development of tumor necrosis factor α (TNFα) inhibitor therapy are the most significant advancements in the treatment of chronic inflammatory diseases like rheumatoid arthritis (RA) and spondyloarthropathies (SpA) [1–4]. Compared with traditional disease modifying anti-rheumatic drugs (DMARDs), the anti-TNFα blockers showed significant efficacy, more rapid onset

Abbreviations: BBB, blood brain barrier; CNS, central nervous system; DMARDs, disease modifying anti-rheumatic drugs; EAE, experimental autoimmune encephalomyelitis; IL, interleukin; INF-γ, interferon γ; MS, multiple sclerosis; NOD, nonobese diabetic; RA, rheumatoid arthritis; TACE, TNFα converting enzyme; TNFα, tumor necrosis factor α; TNFR2, TNF receptor; tmTNF, monomeric type-2 transmembrane precursor protein; SpA, spondyloarthropathies; sTNF, soluble form of cytokine.

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http://dx.doi.org/10.1016/j.autrev.2013.09.002

of action, and inhibition of structural damage development [2–6]. As TNFα agents have become increasingly utilized, there have been a number of reports of adverse events [7,8] as well as of nervous systemic involvement in patients receiving anti-TNFα therapy [6,9]. Given the growing use of these agents in every day clinical practice, it is prudent to examine the association between these drugs and neurological disorders, before assuming causality. Several issues should be considered: (i) Does the use of anti-TNFα agents cause nervous system diseases? (ii) Does the use of these drugs unmask latent disease? (iii) Is the use of these agents and the development of neurological disorders coincidental?

The purpose of this review is to deal with the biology of TNFα in the central nervous system (CNS) and examine the association of anti-TNFα therapy with neurological adverse events, especially demyelination.

2. Evidence of neurological involvement after anti-TNF therapy

TNFα antagonists are an established therapeutic option for several inflammatory diseases. Despite their clinical efficacy, neurological adverse events have been reported and recent data suggest a potential role of anti-TNFα in the induction of neurological diseases, especially demyelination of the CNS, as well as peripheral nervous system involvement. The clinical presentation of all of these cases varies and includes altered mental status, paresthesias, dysesthesias, optic neuritis, motor deficiency and others (Table 1) [10–37].

Today, five anti-TNFα blockers have been authorized for clinical use: the soluble TNF receptor 2 (TNFR2), etanercept and the four anti-TNFα specific monoclonal antibodies (infliximab, adalimumab, golimumab and certolizumab). They act by inhibiting the soluble TNFα, preventing its binding on TNF receptors 1 and 2 (TNFR1, R2).

The frequency of CNS demyelination after initiation of anti-TNFα therapy is unknown. Randomized controlled trials and postmarketing studies found a prevalence ranging between 0.05 and 0.2% of the first three anti-TNFα agents to be licensed (infliximab, etanercept, adalimumab) [29]. In a study of Bosch et al., 151 cases of demyelinating CNS processes after anti-TNFα therapy were analyzed [35]. It included optic neuritis (80%) as well as multiple sclerosis (MS) or MS-like disease. Nozak et al. reported seven cases including five cases of peripheral neuropathies [32]. Recently, Andreadou et al. reported four additional demyelinating CNS diseases following anti-TNF therapy [37].

It is estimated that more than two million patients with various chronic inflammatory diseases have been successfully treated with TNFα blockers so far [38]. Several cases of neurological disorders during anti-TNFα therapy have been reported, raising questions about a possible causal association. Although several hypotheses have been proposed in an attempt to explain the possible relationship between TNFα antagonists and demyelination, none is considered to be adequate. The occurrence of demyelination in patients receiving anti-TNFα treatment could be either attributed to the unmasking of a latent preexisting MS, to the emergence of a new demyelination episode, either MS or MS like or finally to incidental coexistence of the two disorders.

3. TNFα biology

TNFα is synthesized as a monomeric type-2 transmembrane precursor protein (tmTNF) which is then cleaved by the TNFα converting enzyme (TACE), releasing the circulating or soluble form of cytokine (sTNF). These monomeric (tmTNF and sTNF) must aggregate into groups of three forming a trimeric TNF [39–41].

Both tmTNF and sTNF are produced by many cells including macrophage, lymphocytes, monocytes, dendritic cells and natural killer cells. In the context of CNS, they are produced by microglia, astrocytes and others. tmTNF and sTNF interact with two distinct TNF receptors: TNFR, TNFR1(p55) and TNFR2(p75) mediating their biological activities [39–41].

sTNFα acts mainly through the TNFR1 causing cell apoptosis, while tmTNF through the TNFR2 leading mainly to cell activation and survival (Fig. 1).

Table 1
Autoimmune disorders after anti-TNFα therapy affecting nervous system.

Central nervous system	Peripheral nervous system
Multiple sclerosis	Guillain–Barre syndrome
Optic neuritis	Miller Fisher syndrome
Acute transverse myelitis	Chronic inflammatory demyelinating polyneuropathy
	Mononeuritis multiplex
	Axonal sensorimotor polyneuropathy
	Multifocal motor neuropathy with conduction block

4. Implication of TNFα in MS

Autopsy studies in MS patients have found high levels of TNFα in the active MS lesions. In addition, high levels of TNFα were observed in cerebrospinal fluid in patients with MS compared to controls and correlated with disease activity and poor outcome. On the other hand, the presence of normal serum levels of this cytokine suggests that in MS patients, TNFα is locally produced by intrathecal cells [42,43].

Several studies demonstrated a pivotal role of TNFα in an animal model of MS, experimental autoimmune encephalomyelitis (EAE). Indeed, treatment with soluble TNFR1–IgG fusion protein or anti-TNF antibodies prevented the development of EAE. In other reports, in TNFα deficient mice, the onset of clinical disease is delayed. However, the rate of disease progression and severity in these mice was comparable to that in wild-type mice, which suggests a more important role of TNFα for disease initiation, but its presence does not seem to be required for disease progression [39–41].

Other studies addressed whether individual TNFRs were involved in different processes of disease progression. In this setting TNFR knockout mice have shown that EAE symptoms were milder or absent in single TNFR1 or double TNFR1 and TNFR2 knockout mice compared with wild type mice. On the other hand, TNFR2 deficient mice showed enhanced disease severity and higher inflammatory response and demyelination. It was also demonstrated the TNFR2 mediated protective actions, such as oligodendrocyte regeneration and lymphocyte suppression. These findings are consistent with divergent TNFRs in CNS autoimmunity. It seems that TNFR1 plays a role in CNS inflammation and demyelination, while TNFR2 acts to limit tissue pathology by suppressing autoreactive CD4+ T cells and macrophages and plays a role in remyelination [39–41].

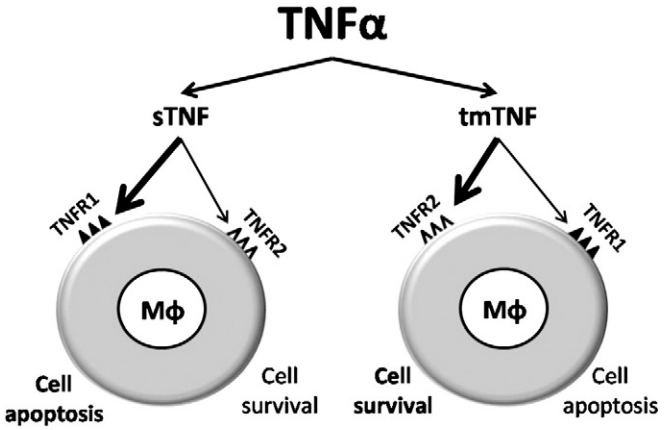

Fig. 1. There are two forms of anti-TNFα: a transmembrane protein (tmTNF) and a soluble form (sTNF). Both interact with two distinct receptors: TNFR1 and TNFR2 but soluble TNF showed greater affinity with TNFR1. It seems that TNFR1, which contains a death domain is responsible for cell apoptosis, while TNFR2 does not contain a death domain and seems to cause cell proliferation and survival.