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The role of biologic therapies in the management of systemic vasculitis

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Abstract

The recent development of biologic therapies capable of selectively targeting components of the immune system has revolutionised the treatment of inflammatory arthritides. The steady increase in use of biologic agents coupled with the expansion in the knowledge of the pathogenesis of vascular inflammation has led to their application in the treatment of primary systemic vasculitis. These agents may have a role in addition to or in place of conventional immunosuppression and also be effective when the latter fails to induce remission. The use of biologics as targeted therapies has also, in reverse, improved our understanding of the pathophysiology of vascular inflammation. While the advent of biologics heralds a new era in the management of the systemic vasculitis, evidence for their efficacy is still in its infancy and has yet to match that of conventional immunosuppressants. In this review, we examine the up-to-date evidence for the use of biologics in systemic vasculitis, including TNF-α inhibitors, and highlight the challenges facing their use. We examine the rationale for using biologics based on the pathophysiology of vasculitis. Issues of toxicity and pharmacovigilance with the use of biologics are also discussed. Finally, future directions and predictions are presented.

Keywords: Biologic agents; Systemic vasculitis; Connective tissue disease; TNF-α; TNF-α inhibitors

Contents

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1. Introduction/background

The treatment of systemic vasculitis has been limited to standard therapies consisting of corticosteroids (CSS) and cytotoxic agents such as cyclophosphamide (CYC). While they remain the mainstay of therapy, in cases of disease relapse and failure to induce remission, newer agents are required. The introduction of biologic agents has revolutionised the treatment of inflammatory arthritides especially rheumatoid arthritis (RA) [1]. Biologics include monoclonal antibodies and DNA engineered vaccines. The initial enthusiasm for the use of TNF-α inhibitors in autoimmune disease was dampened by its use in the treatment of multiple sclerosis (MS) in the early nineties where it resulted in worsening of the disease [2]. Nevertheless, case reports and series on the use of biologics in vasculitis began to emerge in the last few years and large randomised controlled trials such as the Wegener's Granulomatosis Etanercept Trial (WGET) [3] have signalled a new era in both the understanding and experience of their use. This review will cover the emerging role of biologics in the treatment of systemic vasculitis (summarised in Table 1).

2. Pathophysiology of vasculitis

The underlying mechanisms in systemic vasculitis are likely to be complex and varied but the end result is similar-vessel wall inflammation and necrosis leads to occlusion and loss of tissue or organ function. Cytokines are intimately involved and there is an important potential role for anti-neutrophil cytoplasm antibodies (ANCA), based on their appearance in many forms of small vessel vasculitis and from experimental models demonstrating the ability of ANCA to perpetuate an inflammatory reaction close to endothelium.

Table 1
Summary of efficacy and adverse events related to the use of biologics in the treatment of systemic vasculitis

Disease	Agent	Efficacy[a]	Adverse events[b]	References
Giant cell arteritis	Infliximab	Effective in individual cases	0	Case reports (see text)
	Etanercept		0	Case reports (see text)
Takayasu's arteritis	Anti TNF-α agents (etanercept/infliximab)	+++	0	Hoffman et al. [25]
Polyarteritis nodosa	Type 1 interferons (±plasma exchange)	++++	0	Guillevin et al. [32], case reports (see text)
Kawasaki disease	Infliximab	++++, cessation of fever	+, pulmonary haemorrhage	Burns et al. [34]
Wegener's granulomatosis	Etanercept	+++	0	Stone et al. [4]
		++	+++, solid cancers	WG Etanercept trial [3]
	Infliximab	+++	0	Booth et al. [9], Bartolucci et al. [8], Lamprecht et al. [10]
		+++	+, infections/deaths	
	Rituximab	++++	0	Keogh et al. [11], Eriksson et al. [12]
	Anti-thymocyte globulin	++++	+, infection	Schmitt et al. [13]
Churg-Strauss syndrome	Type 1 interferons	++	0	Tatsis et al. [26], Arbach et al. [40].
Cryoglobulinaemic vasculitis	Infliximab	++	++	Chandesris et al. [35], Bartolucci et al. [8]
	Rituximab	+++	+	Sansonno et al. [39], Zaja et al. [37], Roccatello et al. [38], Koukoulaki et al. [36]

[a] Efficacy of biologics are categorised as percentage of patients (0%=0, 1–25%=+, 26–50%=++, 51–75%=+++, >76%=++++) achieving remission at the end point of the study.

[b] Adverse events are categorised based on the percentage of severe adverse events (0%=0, 1–25%=+, 26–50%=++, 51–75%=+++, >76%=++++) during the study and a note on the type of events that occurred is shown.