

REVIEW

THE ROLE OF TUMOUR NECROSIS FACTOR IN THE PATHOGENESIS OF IMMUNE-MEDIATED DISEASES

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Immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis, psoriatic arthritis, psoriasis, axial spondyloarthropathies, Crohn's disease, ulcerative colitis and juvenile idiopathic arthritis, comprise a group of chronic disorders characterized by an immune-mediated pathogenesis. Although at clinical presentation these diseases appear unrelated, they have been recognized to share similar pathogenic mechanisms. Data from epidemiological and genetic studies further support the concept that IMIDs are interrelated, as they can co-occur in the same patient and share a similar genetic susceptibility. The specific aetiologies of IMIDs remain unknown, but all are known to involve dysregulation of the immune system, including an over-expression of the pro-inflammatory cytokine tumour necrosis factor (TNF). The pivotal role played by TNF in the pathogenesis and pathophysiology of IMIDs has been documented by extensive preclinical and clinical investigations, and confirmed by the efficacy of anti-TNF biotechnological drugs, such as etanercept, infliximab and adalimumab, in the therapeutic management of these disorders. In this narrative review, we discuss the available data on the TNF-dependent pathogenesis of IMIDs and associations among the different disorders. Although much remains to be discovered about the pathogenesis and aetiology of IMIDs, their common inflammatory pathological features may explain why they can be successfully targeted by anti-TNF drugs. Among these, adalimumab, a fully human monoclonal antibody, has been approved for treatment of nine distinct IMID indications and it is likely to become a valuable therapeutic tool for this complex cluster of chronic inflammatory disorders.

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REVIEW 2

ANTI-TNF AGENTS AS THERAPEUTIC CHOICE IN IMMUNE-MEDIATED INFLAMMATORY DISEASES: FOCUS ON ADALIMUMAB

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The complex pathogenesis of immune-mediated inflammatory diseases (IMIDs) has been extensively investigated and dysregulation of cytokines, such as tumour necrosis factor (TNF), has been shown to play a dominant role in the pathogenesis of various IMIDs, such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis and psoriatic arthritis. The subsequent development of biological agents capable of blocking TNF has led to important advances in the pharmacotherapy of such diseases and confirmed the concept of a common pathophysiology among IMIDs with TNF having a predominant role. Five TNF inhibitors have currently been approved for treatment of one or more IMIDs; these include infliximab, etanercept, adalimumab, golimumab and certolizumab pegol. Given the similarities in the pathogenic background of IMIDs, one could expect that anti-TNF agents be similarly effective and with comparable tolerability profiles; however, this may not be the case. Structural and pharmacological differences among the anti-TNF drugs are likely to result in differences in efficacy and tolerability among the agents in the different IMIDs, together with differences in potency, therapeutic dose ranges, dosing regimens, administration routes, and propensity for immunogenicity. Among the five TNF inhibitors approved for treatment of IMIDs, adalimumab has the widest range of indications. Data from controlled clinical trials of adalimumab, showing its excellent efficacy and tolerability in a wide range of indications, are supported by real-world long-term data from observational studies, which confirm the value of adalimumab as a suitable choice in the management of IMIDs.

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REVIEW

ADALIMUMAB IN THE TREATMENT OF IMMUNE-MEDIATED DISEASES

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Tumour necrosis factor (TNF) plays an important role in the pathogenesis of immune-mediated inflammatory diseases (IMIDs). TNF inhibition results in down-regulation of abnormal and progressive inflammatory processes, resulting in rapid and sustained clinical remission, improved quality of life and prevention of target organ damage. Adalimumab is the first fully human monoclonal antibody directed against TNF. In this article, we review the role and cost effectiveness of adalimumab in the treatment of IMIDs in adults and children. The efficacy and tolerability of adalimumab has been demonstrated in patients with a wide range of inflammatory conditions, leading to regulatory approval in rheumatoid arthritis (RA), psoriatic arthritis (PsA), plaque psoriasis, inflammatory bowel diseases (Crohn's disease, ulcerative colitis, paediatric Crohn's disease, and intestinal Behçet's disease), ankylosing spondylitis (AS), axial spondyloarthritis (SpA) and juvenile idiopathic arthritis. The major tolerability issues with adalimumab are class effects, such as injection site reactions and increased risk of infection and lymphoma. As with all anti-TNF agents, adalimumab is immunogenic, although less than infliximab, and some patients receiving long-term adalimumab will develop anti-drug antibodies, causing a loss of response. Comparisons of its clinical utility and cost effectiveness have shown it to be a valid treatment choice in a wide range of patients. Recent data from Italian economic studies show the cost effectiveness of adalimumab to be below the threshold value for health care interventions for most indications. In addition, analysis of indirect costs shows that adalimumab significantly reduces social costs associated

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with RA, PsA, AS, Crohn's disease and psoriasis. The fact that adalimumab has the widest range of approved indications, many often presenting together in the same patient due to the common pathogenesis, may further improve the utility of adalimumab. Current clinical evidence shows adalimumab to be a valuable resource in the management of IMIDs. Further research, designed to identify patients who may benefit most from this drug, will better highlight the role and cost-effectiveness of this versatile TNF inhibitor.