EFFECTS OF SULPHASALAZINE ON LYMPHOCYTE FUNCTIONS

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ABSTRACT


Sulphasalazine (SASP) is established as a second-line drug in the treatment of rheumatoid arthritis (RA) and some of the seronegative spondarthritides. It is not clear whether the parent compound, one of its two main metabolites or a combination is responsible for its therapeutic effect. Much of the drug's action is also unknown. Since RA and the seronegative spondarthropathies all share substantial immunopathology, the immune effects of SASP and/or its main metabolites may play a major part in its action.

This paper reviews:
(1) the clinical evidence for an immune response and the mechanisms underlying this;
(2) the effect of SASP and its main metabolites on lymphocyte numbers and function, and
(3) the immunological studies designed to identify the active components of the drug.

These studies have shown a variety of immunomodulatory effects associated with the parent compound and its major metabolites, sulphapyridine (SP) and 5-aminosalicylic acid. They suggest that the parent compound present in high concentration in the small intestine exerts suppressive effect on the gut-associated lymphoid tissue, and that SP exerts its effects by inhibition of endothelial cell proliferation necessary for angiogenesis. They indicate possible roles for both the parent compound – SASP – and sulphapyridine. Further studies are awaited to elucidate these mechanisms.

Keywords: sulphasalazine, lymphocyte, immunology, rheumatoid arthritis, inflammation

INTRODUCTION

Sulphasalazine (SASP) is now widely accepted as a disease-modifying drug used in the treatment of rheumatoid arthritis (RA) [1–5]. More recently, its beneficial effects have been reported in ankylosing spondylitis [6], psoriatic arthritis [7] and reactive arthritis [8]. The mechanisms by which SASP exerts its antirheumatic effects are, however, not fully elucidated. Neither is it entirely clear which part of the molecule is active. Less than 30% of ingested SASP is absorbed in the small intestine [9,10]. The remaining drug is cleaved by colonic bacteria into sulphapyridine (SP) and 5-aminosalicylic acid (5-ASA). The latter is largely retained in the colon and can only be detected in serum in very small amounts [10–12]. In the colon, 5-ASA is present in high concentrations and has been found to be the therapeutic moiety of SASP when used in ulcerative colitis [13]. In RA, on the other hand, clinical studies have recently suggested that the parent compound SASP, SP or both are responsible for its antirheumatic activity [14,15] while 5-ASA is inactive [16]. Suggested modes of action of SASP include (a) an antibacterial effect in the colon [17]; (b) decreased prostaglandin synthesis [18]; (c) reduced neutrophil superoxide production [19]; and
(d) immunosuppressive activity. As rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and reactive arthritis all share substantial immunopathology and a substantial proportion of these patients respond to SASP, the immunomodulatory effects of the drug have been examined extensively during recent years. This paper reviews these studies.

CLINICAL EVIDENCE OF AN IMMUNE RESPONSE

SASP has been shown to reduce the levels of serum immunoglobulins (IgG,M,A), circulating immune complexes, rheumatoid factor titre and to lead to immunodeficiencies [20,21]. This implies that it directly or indirectly exerts an effect on the immune system. Drug-induced immunodeficiency, such as low serum IgG and IgM levels, panhypogammaglobulinaemia and particularly selective IgA deficiency, are usually associated with a good clinical response. This acquired immune deficiency is consistent with in vitro data showing a direct drug effect on lymphocyte function in normal control subjects as well as RA patients, and so is not merely a result of improvement of disease activity induced by SASP [22]. The mechanisms by which SASP produces these immunodeficiencies is not entirely clear. Ig deficiency results from failure of the B-lymphocytes to undergo terminal differentiation to antibody secreting plasma cells. Several studies in RA and IBD indicate that SASP affects B-cell numbers and function both in vivo and in vitro [22-26]. Comer and Jasin in 1988 demonstrated in an in vitro study that SASP, but not SP or 5-ASA, at pharmacological concentrations inhibited Ig synthesis by B lymphocytes from normal subjects and RA patients [25]. Moreover, SASP also inhibited the synthesis of IgM rheumatoid factor. Similarly, Fujiwara et al. in 1990, showed that SASP had a marked inhibitory effect on production in vitro of antibodies in murine spleen cells [27]; more recent work has also demonstrated that it inhibits the anti-DNA antibody production in autoimmune mice. In contrast, Holdstock et al. in 1982 were unable to demonstrate any effect of SASP or its metabolites on immunoglobulin production by peripheral blood mononuclear cells or suppressor T-cell activity [28]. This may be explained by different methodology or a shorter incubation time. T lymphocyte function, however, was only marginally affected by SASP and its metabolites at concentrations found in the serum of RA patients [22,25,29]. This would suggest a direct effect on B lymphocytes rather than a T-cell- mediated B-cell response. However, the profound therapeutic effects of SASP in these patients with selective IgA deficiency may be indicative of an alternative mode of action. In vitro experiments have shown that immunoglobulin production by peripheral blood mononuclear cells is depressed by SASP at high concentrations (>750 mg/ml) but not at the lower pharmacological concentrations (<100 mg/ml) found in the blood stream [30]. It is known that SASP concentration in the small intestine may reach very high levels [23,31]. It may have considerable immunomodulatory effects on the gut-associated lymphoid tissue [26,31,32] which, in turn, is known to be the predominant site of IgA production. This may explain the SASP-induced IgA deficiency which is the commonest immunodeficiency associated with this drug. Further support for this concept comes from the earlier work of Laursen in 1978 showing that SASP modified immunity by suppressing antibody-producing cells in the intestine and increasing the production of antigen-specific factors able to interfere with binding antibodies to antigen [33].