Bacterial infections during immunosuppression—immunosuppressive agents interfere not only with immune response, but also with polymorphonuclear cell function

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Introduction

It is obvious that immunosuppressive agents interfere with the immune response to infections [1]. It has not been widely appreciated, however, that immunosuppressive drugs also interfere with the function of polymorphonuclear leukocytes (PMNLs). A body of recent data indicates that immunosuppressive agents influence several PMNL functions. This article summarizes the effects of immunosuppressive drugs on PMNLs and discusses their clinical implications.

Do CsA and FK506 affect polymorphonuclear cell function?

In the past it was assumed that azathioprine, CsA and FK506 do not affect neutrophil production and/or function. The results of Janco and English [2] demonstrate that under conditions where CsA completely stops lymphocyte mitogenesis the drug does not adversely influence phorbol ester (PMA)-stimulated superoxide generation and lysozyme release or PMA-stimulated chemiluminescence or adherence of neutrophils. It was concluded that CsA does not increase susceptibility to infection by exerting an undesirable influence on neutrophil function [2]. In contrast, more recent data document that CsA and FK506 inhibit chemotaxis of PMNLs [3,4] and monocytes [5] in response to specific stimuli. FK506 inhibits formylmethionine-leucine-phenylalanine (fMLP)-induced neutrophil chemotaxis on a vitronectin matrix by suppressing release of PMNLs from attachment sites [6]. Both CsA and FK506 inhibit chemotaxis [6] of PMNLs, whereas inhibition of neutrophil chemotaxis has not been demonstrated with FK506 [7].

Hörl et al. [9] demonstrated that CsA inhibits release of elastase and lactoferrin from isolated PMNLs in vitro, but not after in vivo administration. However, in vivo administration of CsA and prednisolone reduces lactoferrin release under certain conditions, e.g. during postoperative stress or haemodialysis therapy [9]. PMNLs of renal-transplant patients contain a markedly higher gelatinase content under immunosuppression than those of healthy subjects (528 ± 83 ng/10^7 cells). In addition, significantly higher collagenase content was measured in PMNLs of renal transplant patients compared to controls [10]. In vitro CsA, but not azathioprine or prednisolone, inhibits gelatinase, collagenase, and lactoferrin release from PMNLs of healthy subjects, stimulated with the chemotactic peptide FMLPNTL (formyl-norleucyl-leucyl-phenylalanine-norleucyl-tyrosyl-leucine) [10].

What are the mechanisms involved?

Wenzel-Seifert et al. [11] studied the effects of cyclosporin A, D, and H on human neutrophil activation induced by chemoattractants and by various substances that circumvent receptor stimulation. Cyclosporine H inhibited superoxide (O_2^-) formation, increase of cytosolic calcium, release of β-glucuronidase and lysozyme as well as aggregation stimulated by the chemotactic peptide FMLP. Cyclosporin A and D were considerably less effective in inhibiting FMLP-induced O_2^- formation by PMNLs. Both cyclosporins had no effect on exocytosis, rise in cytosolic calcium, and aggregation induced by the chemotactic peptide [11]. In contrast, Taylor et al. [12] found increased granulocyte aggregation in renal transplant patients receiving CsA. Cyclosporin interferes not only with receptor-mediated, but also non-receptor-mediated action.

In the study of Kharazmi et al. [13] CsA at therapeutic blood level concentrations had no effect on neutrophil and monocyte chemotaxis, neutrophil oxidative burst, monocyte phagocytosis, or neutrophil bactericidal activity. Cyclosporin A by itself at a concentration of 4 μM strongly inhibited growth of S. aureus. The calcium ionophore A 23187-induced lactoferrin release was inhibited by treatment of PMNLs with 4 μM CsA, whereas release of lactoferrin from zymosan- or phorbol-ester-activated PMNLs was not affected by the same concentration of CsA [13]. In the study of Pigatto et al. [14] PMNL chemotaxis of CsA-treated patients decreased by 15% after 1 week, by 21% after 2 weeks, and by 12% after 4 weeks, but these changes were not statistically significant. However, in vivo migration of PMNLs decreased significantly during CsA therapy [14]. Kolb et al. [15] could demonstrate a slight but significant negative correlation between CsA blood levels and PMNL chemiluminescence.
ence, suggesting that CsA causes dose-dependent inhibition of phagocytosis. This inhibition was restricted to zymosan stimulation and could not be observed for cells treated with PMA. Weinbaum et al. [16] described slight inhibition of neutrophils during the early phase of phagocytosis as well as slight decrease of microbial killing in vitro after preincubation with CsA. Under immunosuppression the chemiluminescence and superoxide response of PMNLs was decreased in transplant recipients [17]. It was concluded that the impaired oxidative burst by PMNLs may contribute to impaired microbial killing and explain increased morbidity and mortality from infection in renal transplant patients [17]. So much for CsA.

How about corticosteroids?

High doses of corticosteroids inhibit lactoferrin release during contact of blood with a haemodialysis membrane, a known stimulus for PMNL degranulation [8]. Lower doses of corticosteroids in combination with CsA also prevent lactoferrin release from PMNLs during haemodialysis therapy [9].

PMNL agglutination and adherence to vascular endothelial cells may be potentially harmful with respect to cellular host defence against infection. Patients with bacteraemia have a marked increase in PMNL adherence which is reduced by methylprednisolone [20]. These results were confirmed by Bassaris et al. [21] and by Redl et al. [22]. Corticosteroids change the ability of Fc receptors to bind ligands such as chemotactic peptides and prevent the alteration in net PMNL surface charge [21]. However, steroid treatment diminishes the lysosomal enzyme and oxygen radical release from PMNLs and depresses intracellular killing of bacteria and phagocytosis, consequently enhancing the susceptibility to infection [23].

Do monoclonal or polyclonal antibodies affect polymorphonuclear cell function?

PMNL activation occurs in response to the monoclonal antibody OKT3. It has been shown that this antibody is able to induce reactive oxygen intermediate formation in PMNLs when bound to Fc receptor IIB and Fc receptor II. It was suggested that such PMNL activation may in part explain the genesis of initial adverse reactions to OKT3 [24]. In contrast, the administration of polyclonal antilymphocyte sera (ATG/ALG) may result in pancytopenia [25]. Neutropenia after ATG/ALG therapy, however, can effectively be treated by recombinant granulocyte-colony stimulating factor (r-meth HuG-CSF). The study of Schmaldienst et al. [26] demonstrated that episodes of rejection were not induced by G-CSF. Granulocytopenia was cleared within 24 h in most cases. Thus G-CSF therapy appeared to be a safe and effective approach in kidney graft recipients.

Conclusion

Polymorphonuclear cells play an important role in cellular host defence against bacterial infections. The potential side-effects of immunosuppressive drugs interfering with several PMNL functions may explain, at least in part, the enhanced susceptibility for bacterial infections in patients after kidney transplantation. The latter is particularly the case if granulocytopenia supervenes. The above findings provide one more rationale to reduce the dose of these immunosuppressive drugs in renal transplant patients with severe infections.

References

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