Immune Status and Risk for Infection in Patients Receiving Chronic Immunosuppressive Therapy

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ABSTRACT. ***Objective.*** Chronic immunosuppressive therapy may be complicated by infections indicating a more or less profound immune defect. However, immune monitoring to estimate the risk for infection has so far not been performed routinely. The aim of this study was (1) to investigate the effects of commonly used immunosuppressive treatment regimens on lymphocyte subsets and cytokine release from stimulated whole blood cultures in patients with rheumatic or autoimmune diseases; and (2) to determine whether such measurements could be used as predictors of infection, and if so, to determine their predictive value for subsequent infectious complications.

Methods. Patients with various chronic inflammatory diseases (n = 97) treated with different immunosuppressive regimens and healthy controls (n = 36) were evaluated for T lymphocyte subsets and for cytokine release in whole blood cultures after stimulation with lipopolysaccharide (LPS) or phorbol myristate acetate (PMA) and ionomycin.

Results. Therapy with corticosteroids induced dose-dependent lymphocyte depletion. Concomitant application of cytotoxic disease modifying drugs and corticosteroids caused an additive effect on lymphocytopenia, but did not change CD4/CD8 ratio. Corticosteroid therapy was also associated with impaired cytokine release from mononuclear cells in whole blood assays after *in vitro* stimulation with LPS or PMA/ionomycin. Infections requiring hospitalization developed in 19 of 95 evaluable patients during an average followup period of 2.3 years. On logistic regression analysis, lymphocytopenia < 600/µl, in particular < 250 CD4+ T cells/µl, and therapy with corticosteroids > 10 mg prednisolone equivalent per day were predictive of infections. Multiple logistic regression analysis showed that T-helper lymphocytopenia < 250/µl was the best predictor for future infections, with a positive predictive value of 0.53 and a negative predictive value of 0.97.

Conclusion. Patients receiving chronic immunosuppressive therapy can develop severe lymphopenia that involves all subsets. Monitoring T-helper cell counts may be useful to estimate the risk for subsequent infections in such patients. (J Rheumatol 2005;32:1473–80)

Key Indexing Terms:
CHRONIC IMMUNOSUPPRESSIVE THERAPY RHEUMATIC DISEASES
LYMPHOCYTE SUBSETS CYTOKINES WHOLE BLOOD ASSAYS

Cytotoxic drugs and corticosteroids are commonly used to treat autoimmune and rheumatic diseases. Such treatment has beneficial effects on disease progression. Efficacy has been confirmed for the combination of methotrexate with or without corticosteroids in patients with rheumatoid arthritis (RA)[1-3]. Remission can be achieved in patients with connective tissue disease[4] or inflammatory bowel disease[5] using azathioprine alone or in combination with corticosteroids. More severe autoimmune diseases may need the use of more aggressive regimens, such as the combination of high dose corticosteroids and cyclophosphamide for life-threatening vasculitis, first introduced by Fauci, *et al* for the treatment of Wegener's granulomatosis[6]. With high dose corticosteroid and cyclophosphamide treatment, the prognosis of patients with this disease has greatly improved.

However, control of inflammation and autoimmune mechanisms is at the expense of more or less severe immunosuppression, which may lead to infectious complications due to an impaired immune response against infectious agents[7-9]. Bacteria are responsible for the majority of infections in immunocompromised non-neutropenic patients, and the respiratory tract is the organ system affected most often. Infections with pathogens indicating severe T cell deficiency may also occur in these patients, e.g., *Pneumocystis carinii* pneumonia (PCP), and essentially the whole spectrum of opportunistic infections seen as AIDS-defining events in human immunodeficiency virus (HIV)-positive patients has also been observed in patients receiv-

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ing chronic immunosuppressive therapy[8,10,11]. Such "atypical" infections regularly cause diagnostic and therapeutic problems if they occur in HIV-negative persons[12].

The management of HIV-infected patients includes routine determination of the number of peripheral blood CD4-positive T cells to estimate the degree of immunodeficiency and the risk of infection[13,14]. Cutoffs for the initiation of prophylactic antibiotic therapy are well defined for patients with HIV. In contrast, prognostic markers describing the risk for infections in non-neutropenic chronically immunosuppressed patients have not been defined to date. Preliminary data indicate that reduced T-helper counts seem to be a risk factor for infections, such as PCP, for this population as well[10].

Our aim was (1) to investigate the effects of commonly used immunosuppressive treatment regimens on lymphocyte subsets and cytokine release from stimulated whole blood cultures in patients with rheumatic or autoimmune diseases; and (2) to determine whether such measurements could be used as predictors of infection, and if so, to determine their predictive value for subsequent infectious complications.

MATERIALS AND METHODS

Patients and controls. Patients with chronic inflammatory diseases who presented to the outpatient clinic or were treated as inpatients in the internal medicine service of the University of Regensburg Medical Center, Regensburg, Germany, were included into the study between June 1998 and September 1999 (n = 97), if (1) they were taking stable immunosuppressive therapy defined as unchanged doses for at least 4 weeks of disease modifying drugs and corticosteroids at the time of inclusion, and were expected to need longterm immunosuppression; or (2) they had not received immunosuppressive therapy for 3 months before inclusion.

Patients who gave written informed consent to participate were asked to donate 7 ml of blood, which was collected in 3 ml EDTA and 4 ml lithium-heparin anticoagulated syringes (EDTA-Monovette®, Li-Heparin-Monovette®; Sarstedt, Nürnbrecht, Germany) between 8:00 and 11:00 AM. Samples were kept at room temperature until further processing, which was done within 3 h. Demographic data, diagnosis, and type and dose of current immunosuppressive therapy were recorded from the patients.

Voluntary controls (n = 36) in the same age range as the patients were recruited after giving written informed consent from laboratory personnel, physicians, and relatives of the investigators. In order to be included as controls, these were required to fulfill the following characteristics: apparently healthy, with no history of rheumatic disease or immunosuppressive treatment and no sign of infection for at least 4 weeks prior to participation in the study.

White blood cell (WBC) count, differential WBC count, and other measures necessary for the management of their chronic inflammatory diseases were determined routinely in all patients, and WBC count and differential WBC count in controls.

Patients and controls were evaluated for the occurrence of infections requiring treatment as inpatients by repeated questioning during routine office visits, review of charts, and by a standardized telephone interview in October 2000 for all patients and controls. The telephone interview included questions regarding the current immunosuppressive treatment, and whether the patient had been hospitalized in the meantime for treatment of infections. If a patient had died in the meantime, these questions were addressed to his next of kin. If a patient had been hospitalized for an infection, more details on the respective episode (microbiology results, site of infection) were extracted from discharge summaries or chart review and the microbiology results reviewed by an infectious diseases specialist (TG).

The study protocol was approved by the University of Regensburg Medical Faculty ethics committee.

Analysis of T lymphocyte subsets. For analysis of T lymphocyte subsets, 100 µl whole EDTA anticoagulated blood was placed in U-bottom tubes (Falcon 2052, Becton-Dickinson, Heidelberg, Germany) and incubated according to the manufacturer's recommendations with the monoclonal antibodies clone UCHT1 for CD3 (Coulter-Immunotech, Krefeld, Germany), clone 13B8.2 for CD4 (Coulter-Immunotech), and clone B9.11 for CD8 (Coulter-Immunotech) detection. Analysis of CD3 and CD4, CD3 and CD8 was performed using double-labeling. Appropriate isotype antibodies (Coulter-Immunotech) served as controls. After 10 min incubation with the antibodies, red blood cells were lysed with Optilyse® lysing solution (Coulter-Immunotech), the samples were then washed once in phosphate buffered saline and analyzed in a Becton-Dickinson FACScan flow cytometer. Further analysis of listmode data was done on a PC with WinMDI 2.8 flow cytometry software (Scripps Institute, La Jolla, CA, USA). In brief, white blood cells (WBC) were differentiated according to their forward and side light scatter characteristics. Lymphocyte and monocyte regions were gated to histogram or dotplot windows for analysis of positively stained cell populations. Cutoffs were set according to the staining results obtained with isotype controls. Among the lymphocytes, T cells were identified by CD3-positive staining. Absolute numbers of lymphocyte subsets were calculated from total WBC counts, differential WBC counts, and flow cytometry results.

Whole blood assays. Whole blood assays were performed by placing 400 µl of heparin anticoagulated blood together with 1600 µl of endotoxin-free RPMI-1640 medium (Gibco Life Technologies, Karlsruhe, Germany) in sterile 12-well plates (Falcon; Becton Dickinson) and *E. coli* LPS at a final concentration of 10 ng/ml or phorbol myristate acetate (PMA) and ionomycin at final concentrations of 5 ng/ml and 1 µmol/l, respectively, were added (all chemicals from Sigma-Aldrich, Munich, Germany). Incubation with medium alone served as control. The whole blood assays were kept at 37°C in a 5% CO_2 atmosphere. After 24 h the supernatants of the assays were harvested and stored frozen at –20°C until analysis for the cytokines interleukin 6 (IL-6), IL-2, and interferon-γ (IFN-γ) with commercial ELISA-kits (IL-2, IL-6: Coulter-Immunotech; IFN-γ: Endogen, Woburn, MA, USA).

Statistical analysis and data presentation. The data were analyzed by regression analysis using Spearman's correlation coefficient, Wilcoxon rank-sum test, chi-square test, and logistic regression analysis where applicable (SigmaStat 2.03 statistical package; SPSS, Erkrath, Germany). $p \leq 0.05$ was considered significant. For parameters identified to be associated with infections, receiver-operator curves (ROC) were created to calculate the cutoff value with the highest accuracy. Using this cutoff value, sensitivity, specificity, and positive and negative predictive values were determined.

Analyses of infections with respect to immune status and immunosuppressive treatment were referenced for the individual patient to variables and treatment at study entry (i.e., time the immune status was obtained); changes in corticosteroid dose over time were disregarded.

RESULTS

Demographic data. Mean age of the 97 patients and 36 controls was 47.0 (± 17.5) and 41.3 (± 16.1) years (± SD), range 18–83 and 21–81, respectively (p nonsignificant for the comparison); 33% of patients and 44.4% of controls were male (p = NS for the comparison). The diagnoses of the patients (determined according to standard American College of Rheumatology and American Rheumatism Association criteria) and the immunosuppressive regimens

they received at study inclusion (time the immune status was obtained) are listed in Table 1.

Analysis of T lymphocyte subsets and monocytes. Total lymphocyte counts were found to be markedly decreased in patients receiving corticosteroids at doses > 10 mg prednisolone equivalent per day, or combination immunosuppressive therapy with cytotoxic drugs and corticosteroids at various doses (Figure 1A). This effect was most pronounced under treatment with cyclophosphamide and corticosteroids. Treatment with cytotoxic drugs and/or corticosteroids, however, had no significant effect on CD4/CD8 ratio, which was 2.2 for patients under immunosuppressive therapy, 2.56 for patients not receiving immunosuppressive therapy, and 2.1 for controls (differences not significant). CD3+ CD4+ (T-helper) lymphocytes therefore followed the same pattern seen for lymphocytes overall, with a considerable number of patients showing severely decreased T-helper counts (Figure 1B). For monocytes, only a nonsignificant drop with increasing corticosteroid dose could be observed (data not shown).

Analysis of cytokine release in whole blood assays. Release of IL-2 and IFN-γ from whole blood assays after stimulation with PMA/ionomycin was significantly reduced in patients compared to controls, in contrast to release of IL-6 after stimulation with LPS. In patients receiving immunosuppressive therapy, release of IL-2, but not IFN-γ, was significantly lower in those who subsequently developed infections compared to those without infections (comparison of multiple means by ANOVA test; Figure 2A, 2B, 2C).

Patient followup. Followup information from standardized telephone interview and chart review was available for 95 of the 97 patients with chronic inflammatory diseases. Three patients who had not received immunosuppressive therapy at study entry were later given immunosuppressive therapy. One patient stopped immunosuppressive therapy. Four other patients were switched to other immunosuppressive regimens. All these received another immune status analysis after therapy had been switched or initiated, and their followup period for the evaluation of infectious complications was assigned at this timepoint to the new immunosuppressive regimen (or control group, respectively). All other patients continued immunosuppressive therapy with the disease modifying agent (if applicable) or corticosteroid they had received at study inclusion; in several cases, corticosteroid doses were modified over time in accord with disease activity.

Mean followup was 843 (SD 212, median 891) days (2.31 yrs), representing a total followup period of 80,131 patient-days. For patients who died during the observation period, followup periods were calculated until the day they died.

Infections associated with immunosuppressive therapy. Nineteen patients from the cohort were hospitalized for 25 infectious episodes in the time period studied. The responsible pathogens could be identified in 17 of the 25 episodes (68%; Table 2). The hospitalization rate for infectious diseases was calculated as 0.114 per patient-year of followup for the whole cohort (the 2 patients lost to followup not included). No severe infections occurred in the controls or patients who did not receive immunosuppressive therapy. If the analysis was restricted to the subgroup of patients who had received immunosuppressive therapy (67,373 days of followup), a rate of 0.135 hospitalizations for infectious diseases per patient-year of followup was calculated.

Seven patients died during the study period, 3 from noninfectious diseases, and 4 from infectious complications. All of these had received immunosuppressive therapy. This represents an infection related mortality of 0.018 per patient-

Table 1. Basic characteristics of patients and controls.

	Patients	Controls
N	97	36
Female/male	65/32	20/16
Age, years ± SD	47.0 ± 17.5	41.3 ± 16.1
Diagnoses (%)		
Arthritis	26 (26.8)	—
Rheumatoid arthritis	15	—
Psoriatic arthritis	8	—
Spondyloarthritis	3	—
Vasculitis	22 (22.7)	—
Connective tissue diseases	42 (43.3)	—
Inflammatory bowel disease	6 (6.2)	—
Autoimmune hepatitis	1 (1.0)	—
Medication (at study entry)		
Methotrexate ± corticosteroids	31 (32.0)	—
Azathioprine ± corticosteroids	28 (28.9)	—
Cyclophosphamide ± corticosteroids	8 (8.2)	—
Corticosteroids only	13 (13.4)	—
No immunosuppressive therapy	17 (17.5)	—

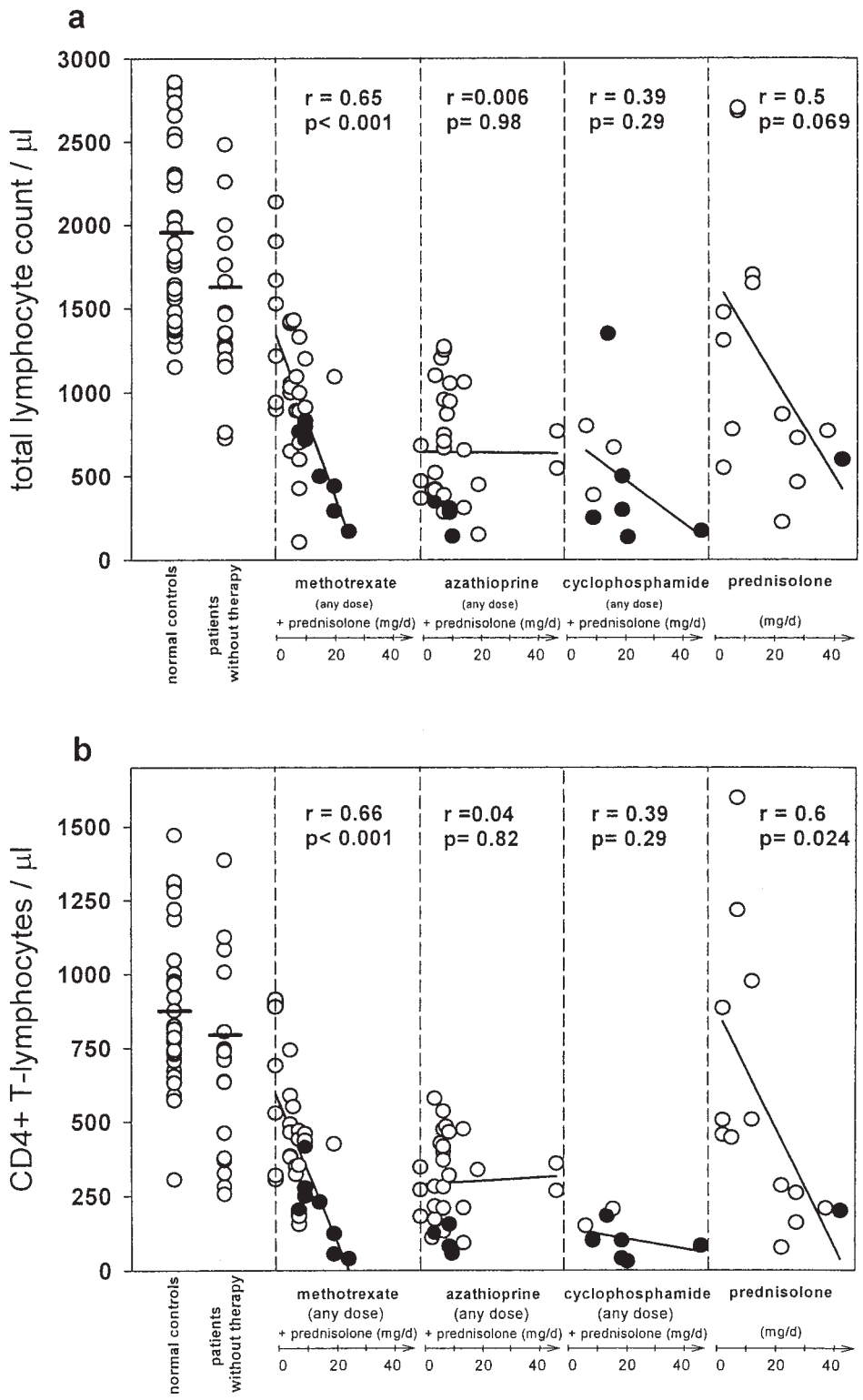

Figure 1. Effects of therapy with cytotoxic drugs and/or prednisolone on total lymphocyte counts (A) and CD4+ T lymphocyte counts (B). Lines indicate means and regression lines, r: Spearman correlation coefficient. ○: patients without infections, ●: patients who later developed infections.

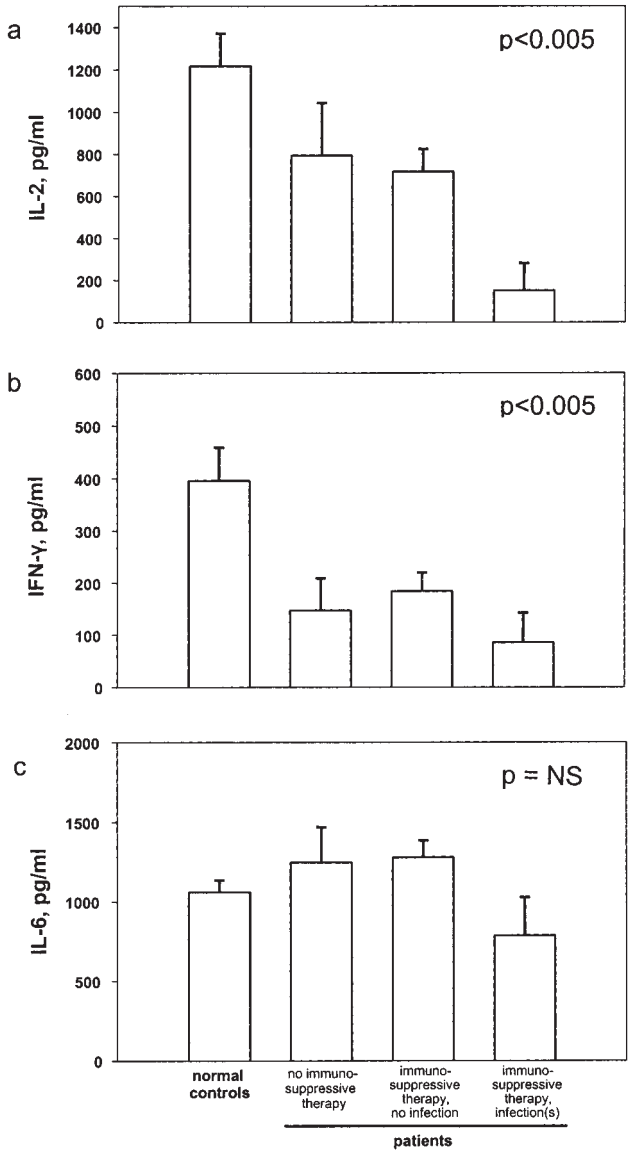

Figure 2. IL-2 and IFN-γ release from whole blood assays after stimulation with PMA/ionomycin (A and B), and IL-6 after stimulation with LPS (C). Data are shown as means ± SEM; comparison of multiple means by ANOVA.

year of followup for the whole cohort and 0.022 for those patients receiving immunosuppressive therapy.

Patients receiving disease modifying therapy with cyclophosphamide with or without corticosteroids experienced infectious complications most often (Table 3); 6 out of the 9 patients receiving such therapy had to be hospitalized for infections during the observation period. Patients receiving methotrexate with or without corticosteroids, azathioprine with or without corticosteroids, or corticosteroids alone had a significantly lower incidence of infections compared to those receiving cyclophosphamide with or without corticosteroids ($p < 0.01$). No significant differences were noted when infection rates were analyzed in relation to underlying rheumatologic diseases (Table 4).

Using logistic regression analysis, corticosteroid dose ($p = 0.012$), absolute lymphocyte count ($p = 0.001$), CD4+ T lymphocyte count ($p < 0.001$), and IL-2 release upon stimulation with PMA/ionomycin ($p < 0.05$) were independent variables significantly associated with hospitalizations for infectious diseases (dependent variable). Figure 3 displays the ROC for these variables. According to the highest accuracy, optimal cutoffs were identified as corticosteroid doses of 10 mg prednisolone equivalent per day, with a sensitivity of 0.74, specificity 0.71, and accuracy 0.72; total lymphocyte counts of 600/µl, with a sensitivity of 0.74, specificity 0.8, and accuracy 0.79; and CD4+ T lymphocyte counts of 250/µl, with a sensitivity of 0.9, specificity 0.82, and accuracy 0.83.

Using these cutoff values, positive predictive values for subsequent infections requiring hospitalization were calculated as 0.44 for corticosteroid doses > 10 mg prednisolone equivalent per day, 0.47 for total lymphocyte count ≤ 600/µl, and 0.53 for CD4+ T lymphocyte count ≤ 250/µl. Negative predictive values for infections requiring hospitalization were 0.89 for corticosteroid doses ≤ 10 mg prednisolone equivalent per day, 0.93 for total lymphocyte count > 600/µl, and 0.97 for CD4+ T lymphocyte count ≥ 250/µl.

Multiple stepwise logistic regression analysis using the variables age, corticosteroid dose, total lymphocyte count, CD4+ T lymphocyte count, CD4+/CD8+ ratio, and release of IL-2 after stimulation of whole blood cultures with PMA/ionomycin revealed that CD4+ T lymphocyte count was the only independent variable predictive of infection ($p = 0.004$).

DISCUSSION

We evaluated methods for immune monitoring of patients receiving immunosuppressive therapy. Our results indicate that immunosuppressive therapy with cytotoxic drugs and/or corticosteroids regularly leads to a more or less profound decrease in all lymphocyte subsets, associated with a marked decrease in release of T cell cytokines upon stimulation with PMA/ionomycin. This is in agreement with previous reports and reflects a desired therapeutic effect. Overall, a correlation between corticosteroid dose and lymphopenia was observed, except for treatment with azathioprine and/or prednisolone, which may be due at least in part to an interindividually highly variable bioavailability of azathioprine. In a substantial proportion of patients receiving therapies with cytotoxic drugs and corticosteroids, absolute lymphocyte counts were found to be less than 600/µl and CD4+ T lymphocyte (T-helper) cell counts less than 250/µl. This was especially the case during treatment with cyclophosphamide and prednisolone. No significant changes, however, were seen in the CD4/CD8 ratios, regardless of the immunosuppressive regimen.

Table 2. Infectious complications in the cohort of patients receiving immunosuppressive therapy (n = 85).

Infections	N (25 total)	Microbiological Isolates
Pneumonia	9 (2*)	*P. carinii* (1 patient), *Strep. pneumoniae* (2 patients), *Pseudomonas aeruginosa* (1 patient), unknown (5 patients)
Spontaneous septic arthritis	3	*S. aureus* (3 patients)
Soft tissue infections (abscess, cellulitis)	3	*S. aureus* (2 patients) Mixed gram pos/gram neg (1 patient)
Herpes zoster	3	*Varicella zoster* virus (3 patients)
CNS infections	2 (1*)	*Listeria monocytogenes* (1 patient), unknown (1 patient)
Other		
Endocarditis	5 (1*)	*S. aureus* (1 patient),
Myocarditis		unknown (1 patient),
Pyelonephritis		*E. coli* (1 patient),
Peritonitis		*Prevotella spp*. (1 patient),
Gastroenteritis		unknown (1 patient)

* Patients who died from infection. CNS: central nervous system.

Table 3. Incidence of infections with respect to immunosuppressive regimens.

Immunosuppressive Regimen	Patients with at Least One Hospitalization for Infection During Followup (%)	Infection Rate per Patient-year of Followup
Methotrexate ± prednisolone	8/34 (23.5)	0.141
Azathioprine ± prednisolone	4/29 (13.8)	0.089
Cyclophosphamide ± prednisolone	6/9 (66.7)	0.561
Prednisolone only	1/13 (7.7)	0.038
No therapy	0/18 (0)	0.0

Table 4. Incidence of infections with respect to diagnoses.

Diagnoses	Patients with at Least One Hospitalization for Infection During Followup (%)	Infection Rate per Patient-year of Followup
Arthritis	5/26 (19)	0.08
Rheumatoid arthritis, n = 15	5/15 (33)	0.15
Psoriatic arthritis, n = 8	0/8 (0)	0.0
Spondyloarthritis, n = 3	0/3 (0)	0.0
Vasculitis	5/22 (23)	0.11
Connective tissue disease	14/41 (34)	0.16
Inflammatory bowel disease	1/6 (17)	0.07
Controls	0/36 (0)	0.0

Decreased T-helper cell counts in the same magnitude are typically seen in patients with advanced HIV infection. HIV-infected individuals with such an immune status are at increased risk for infections typically associated with T cell deficiency, such as PCP, a classic opportunistic infection[13]. Such infections do occur as well in patients receiving immunosuppressive therapy for treatment of chronic inflammatory diseases, and if such patients develop, for example, PCP, T-helper cell counts < 200/µl are typically found, as we and others have reported[10,15]. In contrast to HIV-positive patients, the relation between immune status and risk for infection in patients undergoing chronic immunosuppressive therapy has so far not been studied in detail.

In this cohort, confirmed or presumed bacterial infections were seen more often than opportunistic infections such as *P. carinii*, *Listeria monocytogenes,* or severe Herpes zoster. Similarly to previous reports, we also found that the lungs were affected most often as the site of infection, and that the highest infection rate occurred among patients receiving cyclophosphamide[16,17]. A rate of slightly more than 0.1 infections requiring hospitalization per patient-year of followup closely matches recently published data[18]. Infection related mortality is a serious problem in immunocompromised patients. More than half the deaths in this cohort were attributable to infections, the rate also comparable to previous reports[19].

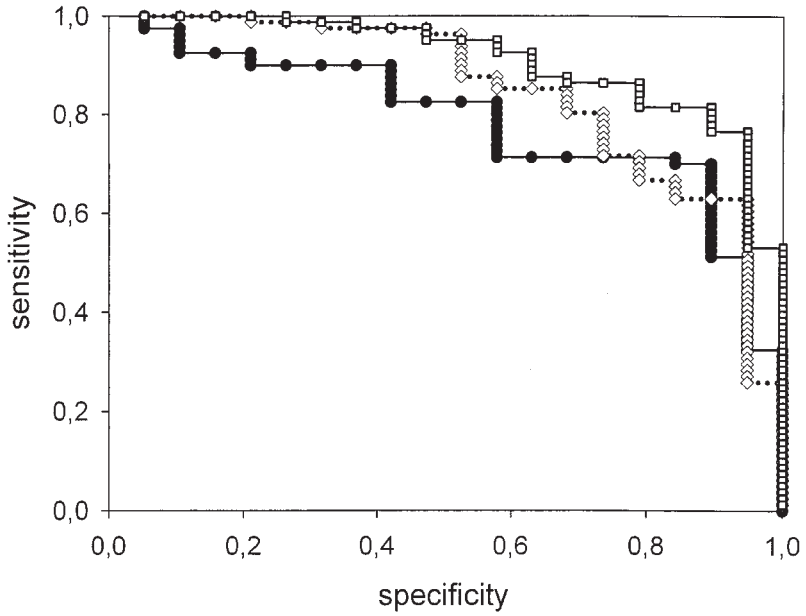

Figure 3. ROC plots for prednisolone dose (●), CD4+ T lymphocyte count (□), and total lymphocyte count (◊) as predictors for infection.

Lymphopenia and corticosteroid dose have already been suggested as risk factors for infections in patients receiving chronic immunosuppressive therapy[20]. Our data confirm these risk factors, but we found that a T-helper lymphocyte count < 250/µl seems to best predict subsequent hospitalizations for infections. This suggests that low T-helper cell counts, regardless of their pathogenesis, can predict infections. Although T cells are typical representatives of the adaptive immune system and are essential to fight viruses and opportunistic pathogens (among others), they seem to play an important role in the defense against bacteria as well.

Cytokine release from "whole blood cultures," after challenge with LPS or PMA/ionomycin, has been repeatedly used to assess functional capacity of mononuclear cells under various conditions[21-24]. While reduced cytokine secretion will ameliorate inflammation in rheumatic diseases, inappropriate IL-2 and IFN-γ secretion may enhance susceptibility to infection. Reduced release of these cytokines was observed in this study, especially in patients who subsequently developed infections. However, whole blood culture assays are complicated to perform, and cytokine release did not turn out to be a good predictor for infections.

This study has some limitations. First, no followup determinations of the immune status in the cohort have been performed. Second, no precise documentation of corticosteroid doses during the followup period was available. This limits the evaluation of the effects that duration of treatment and/or different corticosteroid doses may have had on immune status and risk for infection, and may explain why corticosteroid dose did not prove to be an independent risk factor for infection. Third, it has to be taken into account that rheumatic diseases per se predispose to certain infections. This has been suggested for joint infections in RA, and patients with systemic lupus erythematosus show a generally increased susceptibility for infections[18,19]. The number of patients in this study is too small to evaluate infections in the various treatment groups separately with respect to the patients' underlying rheumatic diseases. When infection rates were analyzed overall with respect to diagnoses, no major differences were noted, in contrast to infection rates in the different treatment groups.

Our results show that the immune defect associated with corticosteroids and cytotoxic drugs used as immunosuppressive treatment for rheumatic and autoimmune disease can be characterized at least in part by lymphocytopenia that involves all subsets, and by impaired cytokine release. In our analysis, a T-helper cell count < 250/µl was the variable that best described the risk for subsequent infections requiring hospitalization. CD4+ T lymphocyte counts associated with infections in this group of patients are in the same magnitude as in HIV-positive patients with increased risk for infections. It can therefore be speculated that, regardless of the pathogenesis leading to depressed T-helper cell counts, this is a useful indicator to assess risk for infections.

We suggest that patients under chronic immunosuppressive therapy, especially those with higher daily corticosteroid doses for longer periods, should be monitored for lymphopenia with T-helper cell counts < 250/µl. The majority of infectious complications in such conditions are caused by bacterial pathogens. Typical opportunistic infections

such as PCP occur more rarely. Antibiotic prophylaxis may be warranted for selected patients receiving chronic immunosuppressive therapy, similar to patients with HIV related immune defect. Future research should determine the efficacy and effectiveness of antibiotic prophylaxis for such patients guided by immune indicators, as has been done for patients with HIV infection.

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