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Rapid Disease Progression in Human Immunodeficiency Virus Type 1–Infected Individuals with Adverse Reactions to Trimethoprim-Sulfamethoxazole Prophylaxis

Jan Veenstra, Paul J. Veugelers, Ireneus P. M. Keet, Andre J. A. M. van der Ven, Frank Miedema, Joep M. A. Lange, and Roel A. Coutinho

We studied the relation between the occurrence of adverse reactions to trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis and the subsequent course of human immunodeficiency virus (HIV) infection in a cohort of homosexual men. Adverse reactions to TMP-SMZ were associated with a more rapid progression to AIDS (P < .001) and death (P < .001) and with a more rapid decline in CD4+ cell counts (P = .001). The median time to progression to AIDS was 14.9 months in subjects with adverse reactions to TMP-SMZ and 32.5 months in those without adverse reactions. After exclusion of Pneumocystis carinii pneumonia (PCP) and toxoplasmosis from the case definition of AIDS, the differences in the rate of progression to AIDS between subjects with and without adverse reactions to TMP-SMZ were still highly significant (P = .004). A low CD4+ cell count at baseline and the use of antiretroviral agents before the start of prophylaxis were predictors of adverse reactions to TMP-SMZ but did not account for the difference in progression to AIDS between subjects with and without adverse reactions to TMP-SMZ. In a univariate analysis, the relative hazard of adverse reactions to TMP-SMZ for progression to AIDS was 2.54 (95% confidence interval [CI], 1.50–4.28); in a multivariate analysis, it was 2.21 (95% CI, 1.29–3.81). The relative hazards of adverse reactions to TMP-SMZ for progression to AIDS with the exclusion of PCP and toxoplasmosis, CD4+ cell counts of <50/mm³, and death were 2.16 (95% CI, 1.25–3.72), 2.37 (95% CI, 1.36–4.12), and 3.21 (95% CI, 1.80–5.72), respectively. It is unclear whether adverse reactions to TMP-SMZ induce or merely predict progression of HIV disease.

Trimethoprim-sulfamethoxazole (TMP-SMZ) is highly effective as treatment and prophylaxis for initial and recurrent episodes of Pneumocystis carinii pneumonia (PCP) [1–3]. In addition to its efficacy in preventing PCP, TMP-SMZ also protects against toxoplasmosis and several bacterial infections [3–5]. Although TMP-SMZ is the preferred drug for prophylaxis for PCP, about one-quarter of HIV type 1 (HIV-1)–infected individuals experience adverse reactions that occur mostly within the first month of treatment [6]. The alternatives, aerosolized pentamidine and oral dapsone, are less effective as prophylaxis for P. carinii infections and toxoplasmosis [7, 8].

We studied the relation between the occurrence of adverse reactions to TMP-SMZ prophylaxis and the subsequent course of HIV infection in a cohort of homosexual men. We found a relatively large difference in survival from the start of PCP prophylaxis to death between HIV-1-infected patients without adverse reactions to TMP-SMZ and those with adverse reactions to TMP-SMZ. Patients with adverse reactions to TMP-SMZ subsequently had a more rapid progression of HIV infection that could only partly be explained by an increased incidence of PCP or toxoplasmosis.

Patients and Methods

Patient population. In 1984, a prospective study on HIV infection and AIDS in sexually active homosexual men was started (The Amsterdam Cohort Study) [9]. HIV-1-seropositive subjects were seen every 3 months; during the visits, a standardized medical history was taken, a physical examination was performed, and blood samples were drawn. Included in our study were AIDS-free HIV-1-infected subjects who participated in the cohort study for at least 1 year before they started...
receiving TMP-SMZ as primary prophylaxis for PCP. The censuring date of our study was 31 August 1995.

**PCP prophylaxis.** Since February 1990, asymptomatic HIV-1-infected subjects were advised to start primary prophylaxis for PCP when they had two consecutive CD4+ cell counts of <200/mm³. In February 1991, the criterion for starting prophylaxis was changed: asymptomatic HIV-1-seropositive subjects were advised to start PCP prophylaxis when they had one CD4+ cell count of <200/mm³.

TMP-SMZ was prescribed as PCP prophylaxis for all patients except three with a history of adverse reactions to TMP-SMZ and seven who participated in an early study of the efficacy of zidovudine, in which only aerosolized pentamidine was allowed as PCP prophylaxis [10]; these 10 subjects were not included in our study. The initial dose of TMP-SMZ was 960 mg once daily. In August 1991, the TMP-SMZ dose was changed to 480 mg, following a randomized trial that showed that the lower dose had an equal clinical efficacy but fewer side effects [2]. Prophylaxis for all subjects who had to stop taking TMP-SMZ because of adverse reactions was changed to aerosolized pentamidine (300 mg once every 4 weeks).

**Comedication.** The administration of drugs that might influence the metabolism of TMP-SMZ and those that were used between the start of TMP-SMZ prophylaxis and the occurrence of adverse events was noted.

**Definitions.** Adverse reactions to TMP-SMZ were defined as follows: fever (temperature of >38.5°C), skin rash, and/or gastrointestinal symptoms occurring within 2 months after starting prophylaxis; an event that resolved when TMP-SMZ treatment was stopped; and the permanent discontinuation of TMP-SMZ treatment. AIDS was defined according to the 1987 revised case definition of the Centers for Disease Control and Prevention [11].

**Laboratory methods.** Peripheral blood mononuclear cells were isolated from heparinized venous blood by using density gradient centrifugation in Ficoll-Hypaque solution (Pharmacia, Piscataway, NJ). Lymphocyte immunophenotyping was determined by flow cytometry. T cell reactivity was measured by stimulating cells with CD3 monoclonal antibody (Central Laboratory of the Red Cross Blood Transfusion Service, Amsterdam) and is expressed in counts per minute (normal T cell reactivity based on the 95% confidence limit, >1,100 counts per minute) [12]. To detect the presence of syncytium-inducing (SI) HIV-1 variants, which are associated with a more rapid decline in CD4+ cell count and a more rapid disease progression [13], peripheral blood mononuclear cells were cocultivated with MT-2 cells [14].

**Statistical methods.** The predictive potential of demographic data and laboratory markers for the occurrence of adverse reactions to TMP-SMZ was evaluated by using logistic regression with likelihood ratio tests (P < .05) in backward and forward selection procedures. Differences in disease progression between men with and men without adverse reactions to TMP-SMZ from the start of TMP-SMZ prophylaxis to AIDS, CD4+ cell counts of <50/mm³, and death were evaluated by using Kaplan-Meier survival methods and logrank statistics.

Differences in progression to AIDS might reflect differences in the efficacy of prophylaxis with TMP-SMZ vs. aerosolized pentamidine. Therefore, the above-mentioned analysis was repeated with (1) the exclusion of PCP and toxoplasmosis from the case definition of AIDS and the use of a subsequent AIDS-defining condition instead and (2) the exclusion of PCP and toxoplasmosis as primary AIDS-defining events entirely. Since the degree of immunodeficiency, the criterion for starting prophylaxis, the dose of TMP-SMZ, and concomitant antiretroviral therapy might be associated with the risk for AIDS and death, we evaluated the effect of adverse reactions to TMP-SMZ by means of Cox regression (proportional hazards models) with adjustments for these factors.

**Results**

Between February 1990 and September 1995, 112 AIDS-free HIV-1-infected men (of whom 84 were HIV-seropositive at entry in the cohort and 28 seroconverted to HIV during follow-up) started receiving TMP-SMZ as primary prophylaxis for PCP. All patients except one were Caucasian. TMP-SMZ prophylaxis was stopped permanently for 33 (29%) of the men because of adverse reactions. Fever and/or skin rash occurred in 31 patients (fever and skin rash, 21; fever only, 5; skin rash only, 5); eight of these 31 patients also had gastrointestinal symptoms. Two of 33 subjects stopped TMP-SMZ prophylaxis because of gastrointestinal symptoms without fever or skin rash.

Adverse reactions to TMP-SMZ occurred at a later stage of HIV infection in the group receiving 480 mg than in the group receiving 960 mg (median of 19 days [range, 7–60 days] vs. median of 15 days [range, 5–46], respectively). Only one of the patients was also being treated with ketoconazole at the start of TMP-SMZ prophylaxis; none of the patients were receiving fluconazole, rifampin, or cimetidine therapy concomitantly. Therefore, the occurrence or absence of adverse reactions to TMP-SMZ cannot be associated with the influence of these drugs on the cytochrome P-450-mediated metabolism of TMP-SMZ. It is unlikely that adverse reactions were attributed to drugs other than TMP-SMZ, since none of the patients started receiving therapy with other drugs between the start of TMP-SMZ prophylaxis and the occurrence of adverse reactions.

Logistic regression was used to determine which variables were predictive of the occurrence of adverse reactions (Table 1). A relatively low CD4+ cell count and repeated CD4+ cell counts of <200/mm³ before the start of TMP-SMZ prophylaxis were found to be predictors for the development of adverse reactions, whereas a decline in the CD4+ cell count in the year before the start of TMP-SMZ prophylaxis, T cell response, and biological virus phenotype were not predictive.
Table 1. Baseline characteristics of HIV-infected patients with and without adverse reactions to TMP-SMZ and their predictive value for the occurrence of adverse reactions.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients without adverse reactions (n = 79)</th>
<th>Patients with adverse reactions (n = 33)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>39.7</td>
<td>39.1</td>
<td>0.33 (0.13–0.83)</td>
</tr>
<tr>
<td>Median CD4⁺ cell count (/mm³)</td>
<td>160</td>
<td>140</td>
<td>0.96 (0.71–1.29)</td>
</tr>
<tr>
<td>Median T cell reactivity (cpm)</td>
<td>570</td>
<td>340</td>
<td>2.19 (0.94–5.08)</td>
</tr>
<tr>
<td>Median annual decline in CD4⁺ cell count (/mm³)</td>
<td>82</td>
<td>105</td>
<td>2.06 (0.72–5.27)</td>
</tr>
<tr>
<td>No. (%) with repeated CD4⁺ cell counts of &lt;200/mm³</td>
<td>39 (49)</td>
<td>25 (76)</td>
<td>3.20 (1.27–8.11)</td>
</tr>
<tr>
<td>No. (%) with SI virus phenotype</td>
<td>8 (10)</td>
<td>19 (58)</td>
<td>1.58 (0.67–3.69)</td>
</tr>
<tr>
<td>No. (%) receiving 960 mg of TMP-SMZ</td>
<td>42 (53)</td>
<td>24 (73)</td>
<td>2.33 (0.92–5.08)</td>
</tr>
<tr>
<td>No. (%) receiving antiretroviral therapy</td>
<td>28 (35)</td>
<td>18 (55)</td>
<td>2.19 (0.94–5.08)</td>
</tr>
</tbody>
</table>

NOTE. cpm = counts per minute; SI = syncytium-inducing; TMP-SMZ = trimethoprim-sulfamethoxazole. ORs express a protective effect for adverse reactions to TMP-SMZ per 100/mm³ in CD4⁺ cell counts and elevations of 1,000 cpm in T cell reactivity. ORs express an increased risk for adverse reactions to TMP-SMZ per decline of 100/mm³ in CD4⁺ cell counts in the year before the start of TMP-SMZ prophylaxis, for repeated CD4⁺ cell counts of <200/mm³, for the presence of SI virus variants, for a high dose of TMP-SMZ (960 mg), and for the use of antiretroviral agents before the start of TMP-SMZ prophylaxis.

A high dose of TMP-SMZ and the use of antiretroviral agents (zidovudine and, for a few patients, zidovudine combined with another nucleoside analogue) before the start of TMP-SMZ prophylaxis were associated with the occurrence of adverse reactions, but these associations were not statistically significant. In a multivariate analysis, after correction for CD4⁺ cell counts, the odds ratio for the use of antiretroviral agents before the start of prophylaxis increased to 2.72 (P = .03).

AIDS developed in 26 (79%) of 33 patients with adverse reactions and in 37 (47%) of 79 patients without reactions to TMP-SMZ (table 2). PCP occurred in one patient who was treated with aerosolized pentamidine and in another patient without adverse reactions to TMP-SMZ who had not taken prophylaxis for several months. Toxoplasmosis of the brain occurred as the first AIDS-defining event in eight (24%) of 33 patients with adverse reactions to TMP-SMZ but in none of the patients without adverse reactions (P < .001).

The association of adverse reactions to TMP-SMZ with progression of HIV disease from the start of TMP-SMZ prophylaxis (baseline) was evaluated by means of Kaplan-Meier survival analysis. Adverse reactions to TMP-SMZ were associated with faster progression to AIDS, death, and CD4⁺ cell counts of <50/mm³ (figure 1). The median time from the start of prophylaxis to progression to AIDS was 14.9 months for subjects with adverse reactions to TMP-SMZ but in none of the patients without adverse reactions. A high dose of the prophylaxis for several months. Toxoplasmosis of the brain occurred as the first AIDS-defining event in eight (24%) of 33 patients with adverse reactions to TMP-SMZ but in none of the patients without adverse reactions (P < .001).

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When PCP and toxoplasmosis were excluded from the case definition of AIDS and a subsequent AIDS-defining condition was used instead, the differences in the rate of progression to AIDS were still highly significant (figure 1). In addition, when patients for whom PCP or toxoplasmosis was the AIDS-defining event were excluded from the analysis, the differences remained significant (P = .004). Thus, the difference in progression to AIDS in patients with and without adverse reactions to TMP-SMZ is not merely a reflection of the prophylactic effect of this therapy on toxoplasmosis.

Cox regression (proportional hazards analysis) was used to determine whether the differences in progression to AIDS between patients with and without adverse reactions to TMP-SMZ could be explained by differences at the start of...
Figure 1. Kaplan-Meier survival curves for HIV-infected patients who did (*dotted lines*) and who did not (*solid lines*) have adverse reactions to prophylaxis with trimethoprim-sulfamethoxazole; the curves show the differences in time to progression to AIDS (*A*), AIDS with the exclusion of *Pneumocystis carinii* pneumonia and toxoplasmosis as AIDS-defining conditions (*B*), the first CD4+ cell count of <50/mm³ (*C*), and death (*D*).

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prophylaxis (table 3). The relative hazard of adverse reactions to TMP-SMZ for progression to AIDS was 2.54 (95% CI, 1.50–4.28). In a univariate analysis, a low CD4+ cell count at the start of TMP-SMZ prophylaxis, repeated CD4+ cell counts of <200/mm³ before the start of prophylaxis, and a low T cell reactivity were also significantly associated with progression to AIDS (table 3). Biological virus phenotype (S1/NS1), the dose of TMP-SMZ, and the use of antiretroviral agents before the start of prophylaxis were not statistically associated with progression to AIDS. The relative hazard of adverse reactions to TMP-SMZ was not substantially altered by controlling for CD4+ cell counts, repeated CD4+ cell counts of <200/mm³, and T cell reactivity at baseline (bivariate analysis; table 3).

Multivariate analysis demonstrated that adverse reactions to TMP-SMZ, a low CD4+ cell count at baseline, a low T cell reactivity, and the use of antiretroviral agents before the start of TMP-SMZ prophylaxis were independently associated with faster progression to AIDS (table 3). Similar associations with adverse reactions were found in an analysis of progression to AIDS with the exclusion of PCP and toxoplasmosis (relative hazard [RH], 2.16; 95% CI, 1.25–3.72), CD4+ cell counts of <50/mm³ (RH, 2.37; 95% CI, 1.36–4.12), and death (RH, 3.21; 95% CI, 1.80–5.72).

**Discussion**

The present study reveals a relationship between the occurrence of adverse reactions to TMP-SMZ and the course of HIV infection. Adverse reactions to TMP-SMZ were associated with a more rapid progression to AIDS and death and with a more rapid decline in CD4+ cell counts. In agreement with the findings of other investigators [3, 5, 15], we observed a significant decrease in the incidence of toxoplasmosis, as the first AIDS-defining event, in patients treated with TMP-SMZ. However, the difference in the rate of progression to AIDS between patients treated with TMP-SMZ and patients treated with aerosolized pentamidine could not be explained by this difference in prophylactic efficacy.

A low CD4+ cell count, repeated CD4+ cell counts of <200/mm³, T cell reactivity at baseline, and, in a multivariate analysis, the use of antiretroviral agents before the start of prophylaxis were also statistically associated with a more rapid
Table 3. Relative hazards for progression to AIDS in HIV-infected men with and without adverse reactions to TMP-SMZ.

<table>
<thead>
<tr>
<th>Analysis, factor</th>
<th>Relative hazard (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate</strong></td>
<td></td>
</tr>
<tr>
<td>Adverse reactions to TMP-SMZ</td>
<td>2.54 (1.50–4.28)</td>
</tr>
<tr>
<td>CD4+ cell count per 100/mm³</td>
<td>0.34 (0.18–0.64)</td>
</tr>
<tr>
<td>Repeated CD4+ cell counts of &lt;200/mm³</td>
<td>2.16 (1.19–3.90)</td>
</tr>
<tr>
<td>T cell reactivity per 1,000 cpm</td>
<td>0.54 (0.34–0.86)</td>
</tr>
<tr>
<td>SI virus phenotype</td>
<td>1.35 (0.81–2.26)</td>
</tr>
<tr>
<td>480-mg dose of TMP-SMZ</td>
<td>0.64 (0.33–1.21)</td>
</tr>
<tr>
<td>Antiretroviral therapy before TMP-SMZ prophylaxis</td>
<td>1.66 (0.98–2.80)</td>
</tr>
<tr>
<td><strong>Bivariate</strong></td>
<td></td>
</tr>
<tr>
<td>Adverse reactions to TMP-SMZ</td>
<td>2.29 (1.33–3.92)</td>
</tr>
<tr>
<td>CD4+ cell count per 100/mm³</td>
<td>0.40 (0.22–0.74)</td>
</tr>
<tr>
<td>Repeated CD4+ cell counts of &lt;200/mm³</td>
<td>2.30 (1.35–3.91)</td>
</tr>
<tr>
<td>T cell reactivity per 1,000 cpm</td>
<td>0.60 (1.54–4.39)</td>
</tr>
<tr>
<td><strong>Multivariate</strong></td>
<td></td>
</tr>
<tr>
<td>Adverse reactions to TMP-SMZ</td>
<td>2.21 (1.29–3.81)</td>
</tr>
<tr>
<td>CD4+ cell count per 100/mm³</td>
<td>0.41 (0.21–0.81)</td>
</tr>
<tr>
<td>T cell reactivity per 1,000 cpm</td>
<td>0.62 (0.40–0.94)</td>
</tr>
<tr>
<td>Antiretroviral therapy before TMP-SMZ prophylaxis</td>
<td>1.97 (1.14–3.41)</td>
</tr>
</tbody>
</table>

NOTE. cpm = counts per minute; SI = syncytium-inducing; TMP-SMZ = trimethoprim-sulfamethoxazole. Relative hazards were determined for the presence of adverse reactions to TMP-SMZ per elevations of 100/mm³ in CD4+ cell counts and elevations of 1,000 cpm in T cell reactivity, for repeated CD4+ cell counts of <200/mm³, for the presence of SI virus variants, for a low dose of TMP-SMZ (480 mg), and for the use of antiretroviral agents before the start of TMP-SMZ prophylaxis.

progression to AIDS and death but did not interfere with the association with adverse reactions. Furthermore, a low CD4+ cell count at baseline, repeated CD4+ cell counts of <200/mm³, and the use of antiretroviral agents before the start of PCP prophylaxis were associated with the occurrence of adverse reactions to TMP-SMZ.

It is highly unlikely that differences in survival and in declines in CD4+ cell counts between patients with and without adverse reactions to TMP-SMZ might be due to a direct effect of TMP-SMZ or aerosolized pentamidine on the progression of HIV-1 infection. In two large prospective trials of TMP-SMZ vs. aerosolized pentamidine as prophylaxis for PCP [3, 15], no significant differences in overall mortality were found, and no differences in declines in CD4+ cell counts were reported. The present study illustrates that differences in survival between treated and untreated individuals that are found in on-treatment analysis of drug efficacy trials may reflect a selection of patients rather than a treatment effect.

In the present study, a relatively low CD4+ cell count at baseline and repeated CD4+ cell counts of <200/mm³ were dependable predictors of adverse reactions to TMP-SMZ. The incidence of rashes due to TMP-SMZ in HIV-infected individuals with CD4+ cell counts of <200/mm³ was higher than that in HIV-infected individuals with higher CD4+ cell counts in one study [16].

Similar results have been observed for HIV-1-infected individuals treated with amoxicillin/clavulanate [17]. However, in a study of HIV-1-positive patients with advanced infection who received high dosages of TMP-SMZ (120 mg/kg·d) during treatment of PCP [18], it was found that adverse reactions occurred more often in patients with high CD8+ or CD4+ cell counts and that adverse reactions could be predicted by a CD4+/CD8+ ratio of >0.10. The latter correlation was not observed by other investigators [19].

It is not clear whether adverse reactions to TMP-SMZ prophylaxis was a predictor of adverse reactions to TMP-SMZ and was also associated with a more rapid progression to AIDS and death. An interaction of zidovudine and TMP-SMZ or a difference in the degree of immunodeficiency, the large difference in the dose of TMP-SMZ, or the presence of active PCP. An increase in the incidence of adverse reactions to TMP-SMZ in early stage HIV disease and a decrease in the incidence of these reactions in late stage HIV disease might explain this discrepancy.

Use of antiretroviral agents before the start of TMP-SMZ prophylaxis was a predictor of adverse reactions to TMP-SMZ and was also associated with a more rapid progression to AIDS and death. An interaction of zidovudine and TMP-SMZ or a difference in the degree of disease progression that is not reflected in CD4+ cell counts might explain the increased risk of adverse events. The transient effect of zidovudine on CD4+ cell counts and disease progression may have already ended in patients who used antiretroviral agents before (median time, 22.7 months) the start of TMP-SMZ prophylaxis, which might explain their shortened survival [20].

It is not clear whether adverse reactions to TMP-SMZ merely indicate or also induce progression of HIV disease. A genetic predisposition for the occurrence of adverse reactions as well as for the progression of HIV disease might explain the association. Adverse reactions to TMP-SMZ may be a marker for biological processes that affect the progression of HIV disease.

Oxidative stress is a potent inducer of both viral activation and DNA damage in infected cells [21, 22] and might be a factor in the progression of HIV disease [23]. Increased levels of oxidized glutathione in CD4+ lymphocytes of HIV-infected individuals have recently been reported [24]; these increased levels indicate increased oxidative stress. Oxidation also generates the unstable hydroxylamine metabolite of sulfamethoxazole, and it has been postulated that this intermediate plays a central role in the development of adverse reactions to TMP-SMZ [25].

An accelerated progression of HIV disease could also have been induced by the occurrence of adverse reactions to TMP-SMZ. The association of fever with skin rash and the lower incidence of adverse reactions to TMP-SMZ in patients treated with corticosteroids [18, 26] suggest that inflammatory cytokines may be involved. Several cytokines can activate...
HIV replication that might lead to an accelerated progression of HIV-1 disease [27]. Alternatively, immunosuppression might be induced by the formation of sulfamethoxazole hydroxyxaline; this metabolite inhibits the activity of natural killer cells [28] and induces a profound suppression of T cell proliferation [29].

In conclusion, adverse reactions to TMP-SMZ were associated with a more rapid progression of HIV-1 infection that could not be explained by the preventive effect of TMP-SMZ on PCP and toxoplasmosis. The degree of immunodeficiency and the use of antiretroviral agents before the start of prophylaxis were predictors of adverse reactions to TMP-SMZ but did not account for the differences in survival. Whether adverse reactions to TMP-SMZ induce or merely indicate progression of HIV-1 infection is unclear.

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References


