TIME PATTERNS OF RECURRENCES AND FACTORS PREDISPOSING FOR A HIGHER RISK OF RECURRENCE OF OCULAR TOXOPLASMOSIS

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Purpose: To ascertain time patterns of recurrences and factors predisposing for a higher risk of recurrence of ocular toxoplasmosis.

Methods: Retrospective observational case series with follow-up examination. Database of 4,381 patients with uveitis was used. Data of 84 patients with ocular toxoplasmosis (sample group) could be included.

Results: Two hundred and eighty active lesions in the first affected eye were detected. The mean number of recurrences per year was 0.29 (standard deviation, 0.24). Median recurrence-free survival time was 2.52 years (95% confidence interval, 2.03–3.02 years). Risk of recurrence was highest in the first year after the most recent episode (26%) implying a decrease with increasing recurrence-free interval. The risk of recurrence decreased with the duration of disease ($P < 0.001$). Treatment of the first active lesion influenced the risk of recurrence ($P = 0.048$). Furthermore, the risk of recurrence was influenced by patient age at the time of the first active lesion ($P = 0.021$) and the most recent episode ($P = 0.002$).

Conclusion: A secondary antibiotic prophylaxis could be discussed 1) during the first year after an active lesion has occurred, especially in case of the first active lesion of ocular toxoplasmosis, and 2) in older patients, especially if primarily infected with *Toxoplasma gondii* at an older age.

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Ocular toxoplasmosis (OT) is the leading cause of posterior uveitis.[1–4] Despite years of extensive research, curative therapy is still not available. Therefore, patients with OT carry a lifetime risk of recurrence. Ocular toxoplasmosis and its recurrences are associated with a substantial risk of vision loss.[5] Thus, time patterns of recurrences and factors predisposing for a higher risk of recurrence constitute important influence on disease management and prognosis. The risk of recurrence seems to be highest directly after the most recent active lesion implying a decrease over time.[6,7] Therefore, patients should be followed up more frequently in the first year after suffering from an active lesion of OT. The age of the patient seems to influence the risk of recurrence. This influence is still controversially discussed in the current literature. Regarding the risk of recurrence in several age groups, various studies achieved contrary results.[5,7–12] For example, Holland et al[7] describe a higher risk of recurrence for patients older than 40 years at the time of the initial diagnosis of OT, whereas Garweg et al[8] assign a higher risk of recurrence to patients younger than 20.9 years at the time of the first manifestation of OT.

To avoid the vision loss associated with recurrences of OT, a secondary antibiotic prophylaxis can be a new management strategy possibly reducing the rate of recurrences as shown by Silveira et al[13] and Felix

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et al.[14] Regarding this new management strategy, Holland[15] demanded that "it will be necessary to identify those patients at a greatest risk for recurrences and to gain a better understanding of the interval during which recurrences are most likely to occur, so that people who would not benefit from treatment will not be exposed unnecessarily to the toxic effect of antimicrobial drugs." Thus, we designed a retrospective observational case series with follow-up examination to investigate the time patterns of recurrences and factors predisposing for a higher risk of recurrence of OT. In this manner, we hope to determine the optimal interval during which a secondary antibiotic prophylaxis would be justified and identify patients with a high risk of recurrence who are suitable for such a new disease management.

Patients and Methods

Data Collection

For our retrospective observational case series with follow-up examination, we used a database of 4,381 patients with uveitis.[16] The patients consulted our Interdisciplinary Uveitis Center between January 2000 and June 2012. As shown in the flow chart of Figure 1, OT was clinically and, in some additional cases, serologically diagnosed in 156 patients. In the rare case of an uncertain clinical picture, the analysis of intraocular fluids (Goldmann–Witmer coefficient) was used for diagnosis. Ninety-six of the 156 patients (61.5%) were female and 60 (38.5%) were male.

The study was approved by the local ethical committee and adhered to the tenets of the Declaration of Helsinki. Patients who had not been examined since May 2011 in our center were invited to a follow-up examination. Of the 104 patients participating in the study (Figure 1), the last follow-up examination was carried out on 65.4% (n = 68) of them in the Interdisciplinary Uveitis Center. The remaining 36 patients (34.6%) were last followed up by their local ophthalmologists or outside hospitals. During the course of disease, patients had been followed up at least once a year and accordingly more often when suffering a recurrence. As part of the follow-up examination, visual acuity was tested, and a slit-lamp examination, perimetry, funduscopy, and a fundus picture were carried out.

All patients participating in the study were asked to complete a questionnaire with special interest on the dates of the first manifestation of OT and recurrences. Furthermore, personal data, such as gender, ethnic background, country of birth, and the drug therapy at the time of the first active lesion were collected. The

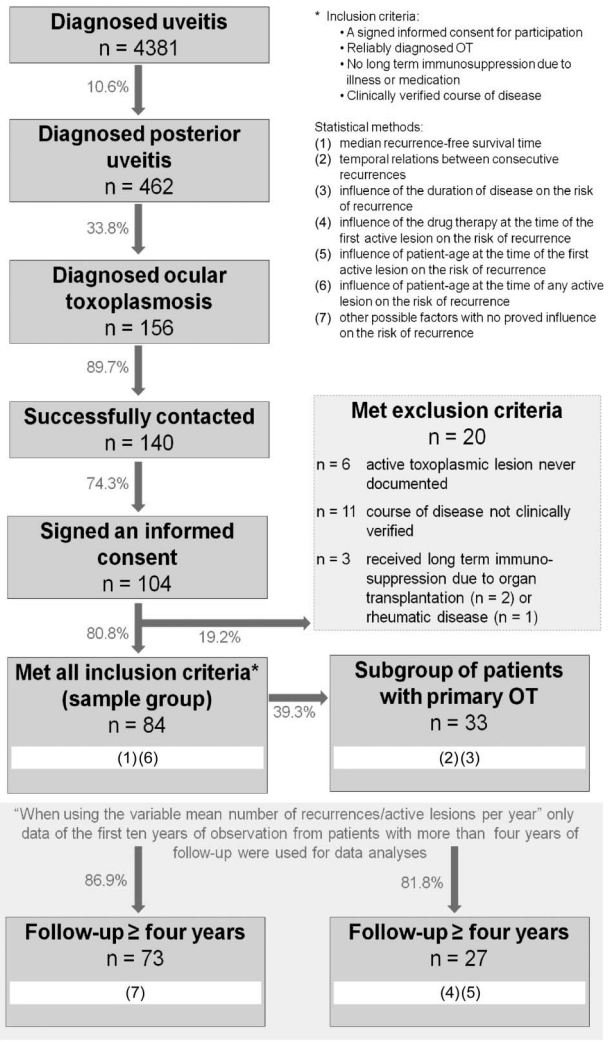

Fig. 1. Flow chart of patients screened and included in the study. Thirty-three of 84 patients of the sample group (39.3%) could be assigned to the subgroup of patients with primary OT. Furthermore, patients with follow-up ≥4 years were extracted from the sample group (n = 73) and from the subgroup of patients with primary OT (n = 27). Also shown is which group of patients (n = 84; n = 73; n = 33; n = 27) was used for each data analysis from (1) to (7).

information received by the questionnaire was compared with the available data of the Interdisciplinary Uveitis Center. Additionally, patients were requested to sign an informed consent permitting to gather information on their course of disease from their local ophthalmologists or outside hospitals they have been followed up. With this data, it was possible to clinically verify information received by the questionnaire and a patient's course of disease.

For reconstructing a patient's course of disease, the following definitions based on the criteria by Holland et al[17] were used: 1) Primary OT was defined as an active retinochoroiditis, called the first active lesion, without a preexisting scar in the same eye. The

constellation of an active lesion without a preexisting scar in the same eye is a strong argument for a primary/acquired infection with *Toxoplasma gondii*.[18] Serology was not routinely performed, therefore serologic criteria for the acute phase of systemic infection with *T. gondii* (the presence of IgM and/or IgA) were not taken into account for diagnosing primary OT[19]; 2) A recurrence was defined as an active lesion in the presence of a retinochoroidal scar in the same eye; and 3) The description of an active lesion does not differentiate between the first active lesions (primary OT) and recurrent lesions. For each active lesion, we determined the age of the patient at the time of diagnosis, the interval to the subsequent recurrence, and the time since the first documented active lesion. The interval from the last documented active lesion to the last follow-up examination was also determined, as well as the patient age at the time of the first diagnosis of OT.

After reconstructing the course of disease for all 104 patients who participated in the study, the exclusion criteria for data analysis were checked (Figure 1). The patients receiving long-term immunosuppression were excluded because of the fact that suppression of the host's defenses causes more severe and more frequent reactivations of OT.[11,20,21] For the same reason, patients infected by HIV would have been excluded.[11,22] The data of the remaining 84 patients (sample group, Figure 1) could be used for analyses. None of the patients received a prophylactic antibiotic treatment. Seventeen of the sample group (20.2%) showed bilateral infection with OT. As in the study of Holland et al[7] for subjects with bilateral disease, only data of the first affected eyes were used for analyses. This measure creates equal conditions for all patients and prevents bias of the results. Thirty-three (39.3%, Figure 1) of the sample group could be assigned to the subgroup of patients with primary OT.

Statistical Methods

SPSS version 20.0 was used for statistical analysis. A P of $\alpha < 0.05$ was considered statistically significant.

For the descriptive data analysis, mean, standard deviation (SD), median values, and minimal and maximal values were calculated. For the calculation of the "mean number of recurrences/active lesions per year," only data of the first 10 years of observation of patients with a follow-up of >4 years were used (n = 73 in the sample group; n = 27 in the subgroup of patients with primary OT; Figure 1). This measure can be justified by the fact that using the variable mean number of recurrences/active lesions per year is only appropriate if there are comparable times of follow-up among study subjects.[15]

Figure 1 additionally shows which of the below listed aspects was analyzed to investigate the time patterns of recurrences and factors predisposing for a higher risk of recurrence. It also shows which group of patients was used for each analysis. The following statistical procedures and tests were used for data analyses:

1. The time intervals between consecutive active lesions and the time intervals between the last documented active lesion and the end of follow-up were used to determine the median recurrence-free survival time using the Kaplan–Meier estimate. To compare differences between the medians of the Kaplan–Meier estimators, the generalized Wilcoxon test was used
2. The generalized Wilcoxon test was used to investigate the temporal relations between consecutive recurrences. Only data of patients with primary OT were used, for them being the only patients from whom the exact date of the first active lesion could be determined
3. To analyze the influence of the duration of disease on the risk of recurrence, the correlation between the time since the first active lesion and the risk of recurrence was investigated. Only for patients with primary OT, the time of a primary infection with *T. gondii* (date of the first active lesion) could be determined, and the complete medical history of OT was known. Therefore, only data of these patients were used for this analysis. The correlation was determined by the Spearman rank correlation coefficient (Spearman's r) and also using linear regression to calculate the line of best fit. The determination (R^2) was calculated to assess the validity of the line of best fit. To calculate the mean number of recurrences per year after the time of the first active lesion, the sum of all recurrences occurring within 1/2 consecutive year(s) was divided by the sum of all patients completely followed up during the corresponding year(s). Because of a low number of detected recurrences within 1 year, the number of recurrences within 2 consecutive years was summed up, leading to a higher validity of the result
4. To investigate the influence of the drug therapy received subsequent to the first active lesion on the risk of recurrence, the patients with primary OT were subdivided into groups regarding their received drug therapy (application for >4 weeks up to a maximum of 8 weeks). The following subgroups were created: 1) *T. gondii*–specific antibiotic treatment, including for example, common antibiotic therapeutic strategies, such as sulfadiazine/pyrimethamine, trimethoprim/sulfamethoxazole, clindamycin, atovaquone, or

azithromycin; 2) corticosteroid monotherapy; 3) no systemic drug therapy; 4) antibiotic treatment without assumed effectiveness against *T. gondii* such as antibiotics not listed above; and 5) drug therapy retrospectively not reconstructable. The Mann–Whitney *U* test was used for analysis

5. To investigate the influence of the patient age at the time of the first active lesion on the risk of recurrence, the age of the patient was plotted against the mean number of active lesions per year. The correlation was calculated using the Spearman's r. The drug therapy received subsequent to the first active lesion seems to be a confounding variable in this analysis. Thus, patients were subdivided into groups regarding their received drug therapy. Only patients with primary OT and a follow-up >4 years were used for this analysis; therefore, the mean number of active lesions per year is in proportional ratio to the mean number of recurrences per year
6. To analyze the correlation between patient age at the time of any active lesion and the time interval to the subsequent recurrence, the Spearman's r was used
7. To investigate the influence of other demographic data, such as gender, ethnic background, country of birth, or unilateral versus bilateral presentation on the mean number of recurrences per year, the Mann–Whitney *U* test was used wherever appropriate.

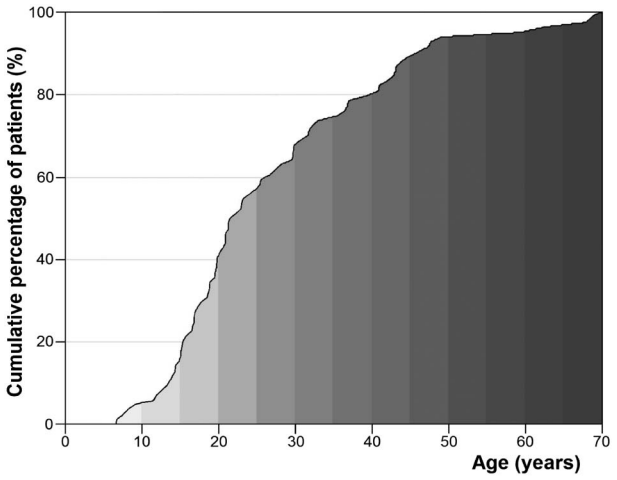

Fig. 2. Patient age at the time of the initial diagnosis of OT. Cumulative percentage of patients of the sample group (n = 84) as a function of patient age at the time of the first presentation with OT to an ophthalmologist.

Results

Part 1—Presentation of the Sample Group and the Subgroup of Patients With Primary Ocular Toxoplasmosis

General characteristics. The sample group was formed by 84 patients, including 57 women (67.5%) and 27 men (32.5%). The mean age at the time of data collection was 40.44 years (SD, 15.03 years; median, 36.96 years; range, 17.89–74.34 years) and 27.19 years at the time of the initial diagnosis of OT (SD, 14.46 years; median, 21.84 years; range, 6.67–69.68 years; Figure 2). At the time of the initial diagnosis, 80.4% of the patients were younger than 40 years (Figure 2). The patients in the sample group were followed a mean of 11.36 years (SD, 9.50 years; median, 8.84 years; range, 1.30–55.55 years).

Thirty-three patients of the sample group (39%) could be assigned to the subgroup of patients with primary OT. Serology was not routinely performed, thus serology was only available for 12 of these patients. Five of these 12 patients (41.7%) had the serologic characteristics of the acute phase of toxoplasmosis (IgM antibodies). In the subgroup of patients with primary OT, 72.7% were women (n = 24) and 27.3% were men (n = 9). The mean age at the time of data collection was 40.83 years (SD, 16.63 years; median, 34.58 years; range, 17.89–74.34 years) and 30.46 years at the time of the initial diagnosis of OT (SD, 17.41 years; median, 24.96 years; range, 7.51–69.68 years). Patients in the subgroup of patients with primary OT were followed a mean of 10.59 years (SD, 9.94 years; median, 7.89 years; range, 1.30–55.55 years).

Mean number of active lesions and mean number of recurrences per year. A total of 289 active lesions were counted. Two hundred and eighty of them occurred in the first affected eye and could therefore be used for data analyses. The mean number of active lesions for all patients in the sample group was 3.22 (SD, 3.42; median, 2; range, 1–27). One patient suffered 27 active lesions, whereas all other patients showed between 1 to 11 active lesions. Because long-term immunosuppression was an exclusion criterion, such an unusual high number of active lesions suffered by one patient cannot be explained at this point. In the subgroup of patients with primary OT, 110 active lesions were counted in total, leading to a mean of 3.33 active lesions per patient (SD, 2.47; median, 3; range, 1–11).

The mean number of recurrences per year was 0.29 in the sample group (n = 73; SD, 0.24; median, 0.26; range, 0.00–1.50) and 0.24 in the subgroup of patients

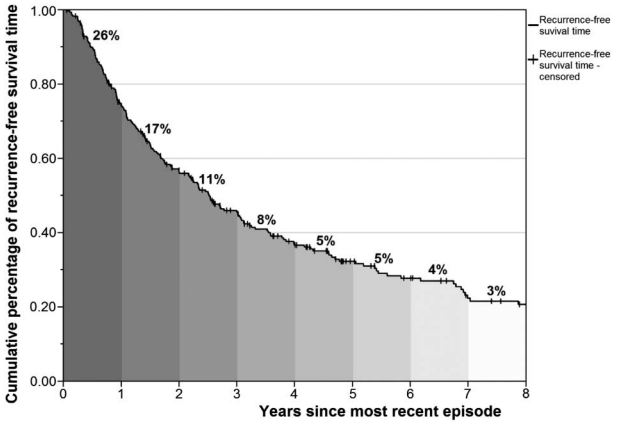

Fig. 3. Recurrence-free survival time. Data of 84 patients (sample group) were used for the analysis, including 196 intervals between consecutive active lesions and 83 intervals from the last documented active lesion to the time of the last follow-up examination. The median recurrence-free survival time, determined by using the Kaplan–Meier estimator, was 2.52 years (95% confidence interval, 2.03–3.02 years). The figure shows 186 recurrences and 70 intervals from the last documented active lesion to the time of the last follow-up examination (recurrence-free survival time–censored) during the first 8 years after the most recent active lesion. The risk of recurrence in each year after the most recent active lesion is additionally given.

with primary OT (n = 27; SD, 0.20; median, 0.20; range, 0.00–0.63).

Part 2—Time Patterns of Recurrences

Recurrence-free survival time. The median recurrence-free survival time was 2.52 years (95% confidence interval, 2.03–3.02 years). The Kaplan–Meier curve of the first 8 years after the most recent active lesion is shown in Figure 3. The Kaplan–Meier curve demonstrates that the risk of recurrence is highest in the first year after the most recent active lesion, implying a decrease with increasing recurrence-free survival time.

To minimize the confounding variable of different follow-up times among study subjects, a similar calculation as shown in Figure 3 was created, only including data during the patients' first 10 years of follow-up (data not listed in detail). No difference between the median recurrence-free survival time of the data analysis using data of the complete follow-up compared with the data analysis using only data during the patients' first 10 years of follow-up could be detected ($P = 0.529$), confirming the general validity of Figure 3.

Temporal relations between consecutive recurrences. The Kaplan–Meier estimates of the time intervals between the first active lesion and the first four recurrences of patients with primary OT were determined. There was no temporal correlation between consecutive recurrences ($P = 0.899$; Table 1).

Influence of the duration of disease on the risk of recurrence. A clear negative correlation between the number of recurrences per year and the duration of disease is shown using the data within 1 year and within 2 consecutive years (1 year [○]: Spearman's r, −0.59, $P = 0.045$; 2 consecutive years [■]: Spearman's r, −0.99, $P < 0.001$; Figure 4). The line of best fit $f(x) = 0.31 - 0.01x$ in Figure 4 is applicable for the number of recurrences within 1 year ($R^2 = 0.36$) and 2 consecutive years ($R^2 = 0.98$). An influence of the duration of disease on the risk of recurrence can be shown. In consequence, the risk of recurrence seems to be highest directly after the first active lesion of OT, implying a decrease over the duration of disease.

Part 3—Factors Potentially Predisposing for a Higher Risk of Recurrence

Influence of drug therapy at the time of the first active lesion on the risk of recurrence. Patients of the subgroup with primary OT (n = 33) were subdivided into groups regarding their received drug therapy subsequent to their first active lesion (Table 2). Eighteen patients received *T. gondii*–specific antibiotic treatment. Seven patients receiving corticosteroid monotherapy because of suspected noninfectious uveitis were treated by outside hospitals or local ophthalmologists. Two patients received antibiotic treatment

Table 1. Temporal Relations Between Consecutive Recurrences

Interval*	No. Recurrences	No. Censored Cases†	Median Recurrence-free Survival Time Years (95% Confidence Interval)	*P*‡
First	24	9	3.07 (2.29–3.85)	0.899
Second	19	5	1.75 (0.83–2.66)	
Third	14	5	2.34 (1.19–3.48)	
Fourth	8	6	2.55 (1.67–3.43)	

Data of patients with primary OT were used for analysis (n = 33).

*Intervals between consecutive recurrences: the first interval from the first active lesion to the first documented recurrence, the second interval from the first to the second documented recurrence, etc.

†Intervals from the last documented active lesion to the time of the last follow-up examination.

‡To investigate temporal relations; generalized Wilcoxon test was used; *P* of $\alpha < 0.05$ was considered significant.

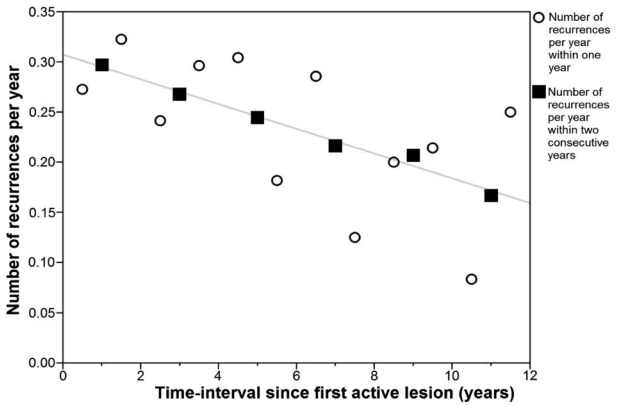

Fig. 4. Influence of the duration of disease on the risk of recurrence. The number of recurrences per year within the corresponding year (○) and 2 consecutive years (■) after the time of the first active lesion is used for analysis. The line of best fit f(x) = 0.31 − 0.01x was calculated using the linear regression ([○]: $R^2 = 0.36$; [■]: $R^2 = 0.98$). The correlation between the number of recurrences per year and the duration of disease was determined using the Spearman rank correlation coefficient ([○]: Spearman's r, −0.59, $P = 0.045$; [■]: Spearman's r, −0.99, $P < 0.001$). Only data of patients with primary OT (n = 33) were used for this analysis.

without assumed effectiveness against *T. gondii*. Four patients receiving no systemic drug therapy were first seen by other ophthalmologists.

To analyze the influence of the drug therapy subsequent to the first active lesion on the risk of recurrence (Table 3), we had to exclude 5 patients of the subgroup with primary OT (n = 33) because of being followed up <4 years. Thus, groups in Table 3 are smaller than in Table 2.

With a mean of 7.99 years of follow-up (SD, 1.99 years; range, 4.55–10.00 years) and 21 detected recurrences (mean, 1.4; SD, 1.59; median, 1; range, 0–4), the group of 15 patients treated with *T. gondii*–specific antibiotics showed a mean of 0.17 recurrences per year (SD, 0.19).

Correspondingly, 5 patients receiving only oral corticosteroids were followed up a mean of 7.76 years (SD, 3.08 years; range, 4.06–10.00 years). Seventeen recurrences were detected (mean, 3.4; SD, 1.67; median, 3; range, 2–6), leading to a mean number of 0.47 recurrences per year (SD, 0.17).

The 3 patients receiving no systemic drug therapy were followed up a mean of 9.07 years (SD, 1.61 years; range, 7.21–10.00 years). Five recurrences were detected (mean, 1.67; SD, 1.15; median, 1; range, 1–3). This leads to a mean number of 0.18 recurrences per year (SD, 0.11).

Although numbers in the groups are small, an effect of increased number of recurrence per year after corticosteroid monotherapy compared with *T. gondii*–specific antibiotic treatment could be shown ($P = 0.048$, Table 3). Because of an even smaller number of patients receiving no systemic drug therapy (n = 3), the significance of the Mann–Whitney *U* test is difficult to judge. No apparent effect between the group of patients receiving no systemic drug therapy compared with patients receiving *T. gondii*–specific antibiotic treatment could be shown ($P = 0.582$, Table 3).

Influence of patient age at the time of the first active lesion on the risk of recurrence. The total number of active lesions at a given patient age is shown in Figure 5. The mean age at an active lesion was 33.19 years (n = 280; SD, 14.27 years; median, 31.78 years; range, 7.51–71.53 years). One hundred and eighty-nine of all 280 documented active lesions (67.5%) in the first affected eye occurred in patients younger than 40 years. Based on the data shown in Figure 5, it could be suspected that younger age is associated with a higher risk of recurrence. However, it should be noted that 80.4% of all patients were younger than 40 years when OT became a manifest (Figure 2). Therefore, the patient age at the time of the first active lesion was plotted against the mean number of active lesions per year in the first 10 years of follow-up (Figure 6). As shown in Table 3, the drug therapy received subsequent to the first active lesion influences the mean number of recurrences per year. Thus, the drug therapy received subsequent to the first active lesion seems to be a confounding variable in analyzing the influence of patient age at the time of the first active lesion on the risk of recurrence. Therefore, the correlation between patient age at the time of the first active lesion and the mean number of active lesions per year in the first 10 years of follow-up was analyzed separately in subgroups of patients regarding their received drug therapy. The correlation was analyzed in the subgroups of patients receiving *T. gondii*–specific antibiotic treatment (n = 15, Spearman's r, 0.59, $P = 0.021$) and corticosteroid monotherapy (n = 5, Spearman's r, 0.90, $P = 0.037$). Because of the low number of patients receiving antibiotic treatment without assumed effectiveness against *T. gondii* (n = 2) or no systemic drug therapy (n = 3), Spearman's r was not calculated in those groups. In conclusion, Figure 6 shows that the risk of recurrence seems to be influenced by the patient age at the time of the first active lesion. Older age at the time of the first active lesion is associated with a higher risk of recurrence.

Influence of patient-age at the time of any active lesion on the risk of recurrence. Regarding the result of Figure 6, it seems to be likely that the risk of recurrence after any active lesion is also influenced by the patient age. To confirm this assumption, the patient age at the time of any active lesion was plotted against the time interval to the subsequent recurrence (Spearman's r, −0.22; $P = 0.002$; Figure 7). In conclusion, it could

Table 2. Drug Therapy Subsequent to the First Active Lesion of Primary OT

Drug Therapy at the Time of First Active Lesion	No. patients (%) (n = 33)
Toxoplasma gondii–specific antibiotic treatment*	**18 (54.5)**
Clindamycin (4 × 300 mg/day)	2 (6.1)
Clindamycin (4 × 300 mg/day) + prednisone	15 (45.4)
Combination of trimethoprim (800 mg) and sulfamethoxazole (160 mg) (4 × 1 tablet/day) + folinic acid + prednisone	1 (3.0)
Corticosteroid monotherapy	**7 (21.2)**
Oral prednisone (initial 100 mg for 2–5 days; dose reduction within the following weeks)	6 (18.2)
Intravenous prednisone (initial 100 mg for 4 days, then change to oral prednisone [80 mg]; dose reduction within the following weeks)	1 (3.0)
No systemic drug therapy	**4 (12.1)**
Antibiotic treatment without assumed effectiveness against *T. gondii*	**2 (6.1)**
Gentamycin	1 (3.0)
Doxycycline	1 (3.0)
Medical treatment retrospectively not reconstructable	**2 (6.1)**

*Including common antibiotic therapeutic strategies against *T. gondii*, such as sulfadiazine/pyrimethamine, trimethoprim/sulphamethoxazole, clindamycin, atovaquone, and azithromycin.

be shown that the risk of recurrence is influenced by the patient's age at the time of the first active lesion (Figure 6) and age at the time of any active lesion (Figure 7).

Other possible factors with no apparent influence on the risk of recurrence. Demographic data as gender, ethnic background, country of birth, or unilateral versus bilateral presentation seem to have no influence on the mean number of recurrences per year ($P > 0.190$; data not listed in detail).

Discussion

Patients with OT are assumed to possess a lifetime risk of recurrence due to tissue cysts remaining in the retina after the initial infection with *T. gondii*.[23,24] Unfortunately, none of the antibiotic drugs used for OT treatment are able to penetrate the cyst walls in the human body and thus are not effective against bradyzoites of *T. gondii*.[25] Therefore, short-term treatment of an active lesion of OT does not prevent recurrences and associated vision loss.[17,26–28] In contrast, a secondary antibiotic prophylaxis can be a new management strategy of OT, which may reduce the rate of recurrences[15] as shown by Silveira et al[13] and Felix et al.[14] To conclusively prove the effect of a secondary antibiotic prophylaxis, further studies will be needed.

Because a secondary antibiotic prophylaxis may reduce the risk of recurrence and therefore can prevent vision loss, the aim of our study was to determine the optimal interval during which a secondary antibiotic prophylaxis would be justified and to identify patients with a high risk of recurrence who will benefit from this new disease management.

The Interval During Which a Secondary Antibiotic Prophylaxis Could Be Justified

The risk of recurrence is highest in the first year after the most recent episode, implying a decrease over the recurrence-free survival time (Figure 3). The highest risk of recurrence directly after an episode was also shown by Holland et al.[7] Two confounding variables possibly influence this result. One, the potential temporal relation between consecutive recurrences as shown by Garweg et al.[8] Two, the fact that patients

Table 3. Influence of Drug Therapy Subsequent to the First Active Lesion on the Risk of Recurrence Within the First 10 Years of Disease

Received Drug Therapy Subsequent to the First Active Lesion	n (%)	No. Recurrences Per Year			*P**
		Mean	SD	Median	
Toxoplasma gondii–specific antibiotic treatment†	15 (55.6)	0.17	0.19	0.13	(1) (2)
Corticosteroid monotherapy	5 (18.5)	0.47	0.17	0.49	(1) (3)
No systemic drug therapy	3 (11.1)	0.18	0.11	0.14	(2) (3)
Antibiotic treatment without assumed effectiveness against *T. gondii*	2 (7.4)	0.30	0.14	0.30	
Medical treatment retrospectively not reconstructable	2 (7.4)	0.20	0.14	0.20	

Data of patients with primary OT and follow-up >4 years were used (n = 27).
*Mann–Whitney *U* test was used for analyses; *P* of $\alpha < 0.05$ was considered significant.
†Including common antibiotic therapeutic strategies against *T. gondii*, such as sulfadiazine/pyrimethamine, trimethoprim/sulphamethoxazole, clindamycin, atovaquone, and azithromycin.

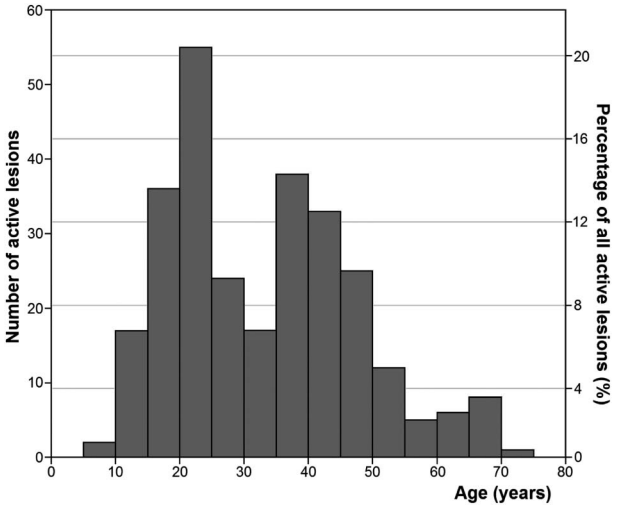

Fig. 5. The figure shows the number of active lesions of OT at a given patient age and the total number of documented active lesions in the first affected eye (n = 280) in 84 patients of the sample group according to patient age during the episode.

with a longer follow-up and therefore with a possible higher absolute number of recurrences take a higher weighting in Figure 3. Contrary to the results of Garweg et al,[8] our study could not show a temporal correlation between consecutive recurrences (Table 1). Therefore, the first mentioned confounding variable seems to be unlikely. To investigate the influence of the second confounding variable, a further calculation only including patients' data of the first 10 years of follow-up was created. In this calculation, the same

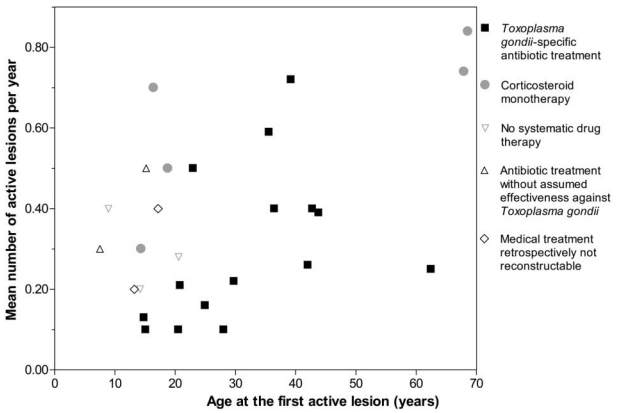

Fig. 6. Older age at the time of the first active lesion is associated with a higher risk of recurrence (the mean number of active lesions per year). Patients with primary OT and a follow-up of >4 years were considered for the analysis, including only the data of the first 10 years of disease (n = 27). For the analysis of correlation between patient age at the time of the first active lesion and the number of active lesions per year, the Spearman rank correlation coefficient (Spearman's r) was used. The correlation was determined separately in groups (n ≥ 5 patients) regarding received drug therapy at the time of the first active lesion: patients receiving *Toxoplasma gondii*–specific antibiotic treatment (n = 15; Spearman's r, 0.60; $P = 0.021$), and patients receiving corticosteroid monotherapy (n = 5; Spearman's r, 0.90; $P = 0.037$).

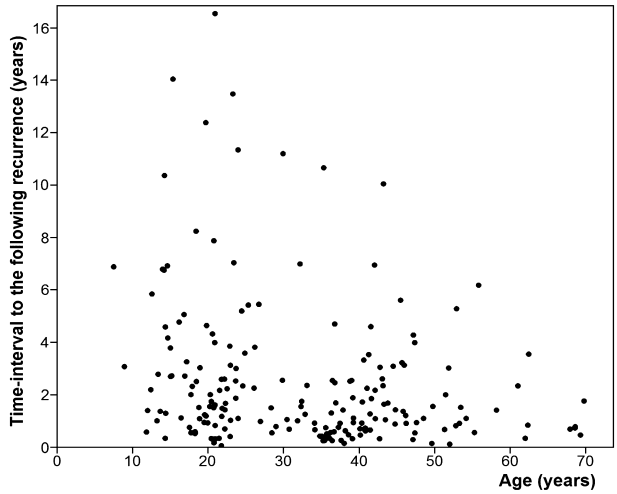

Fig. 7. Patient age at the time of any active lesion influences the risk of recurrence. Data of 84 patients (sample group) with a total of 280 active lesions and 196 intervals from the active lesion to the subsequent recurrence were used for the analysis. The correlation between patient age at the time of any active lesion and the time interval to the subsequent recurrence was determined using the Spearman rank correlation coefficient (Spearman's r, −0.22; $P = 0.002$).

time-dependent distribution of the risk of recurrence as in Figure 3 could be shown. Thus, a general validity of the results in Figure 3 can be assumed for all patients included in this study. The limitation of this analysis is the nonuniform treatment of patients with an active lesion, which cannot be specified because medical treatment was retrospectively not determined for all active lesions. Only the medical treatment for the first diagnosis/first active lesion of OT was determined in this study. Despite this limitation, the first year after an active lesion (even perhaps the first 2 years) could be defined as an interval during which a secondary antibiotic prophylaxis could be justified.

Influence of the Duration of Disease on the Risk of Recurrence

The influence of disease duration on the risk of recurrence was already described by Holland et al.[7] Despite of a limited amount of data when using only data of patients with primary OT, this influence could be confirmed by our study (Figure 4). To analyze the influence of the disease duration on the risk of recurrence using only data of patients with primary OT is appropriate. Only for these patients, the time of the first active lesion is known and therefore the exact duration of disease can be determined. The rate of 39.3% of patients with primary OT in our study is similar to the rate of 28% found by Bosch-Driessen et al.[9] Of the 12 patients for whom serology was available, 41.7% had serologic characteristics of the acute

phase of toxoplasmosis, which is also comparable with the rate of 38% found by Bosch-Driessen et al.[9]

From our data, we can make a prognosis about the probability of a recurrence if the duration of the disease is known. However, it should be mentioned that this result is based on a small patient population. Therefore, further studies with bigger patient numbers will be necessary. Also it should be mentioned that the risk of recurrence is additionally influenced by other host-specific and parasite-specific factors.[15] Therefore, the result should be used with caution to make prognoses in the daily clinical practice. Patients at the beginning of disease possess the highest risk of recurrence. The longer the disease persists, the lower the risk of recurrence becomes. Thus, a secondary antibiotic prophylaxis could be justified for patients suffering their first active lesion of OT (primary OT) or being infected in the recent past.

Influence of Patient Age on the Risk of Recurrence

The influence of patient age is controversially discussed in the literature.[5,7–12] Although Garweg et al[8] assign a higher risk of recurrence to patients younger than 20.9 years at the time of the first manifestation of OT in a data set of 63 patients, Holland et al[7] describe a higher risk of recurrence for patients older than 40 years at the time of the initial diagnosis of OT in a data set of 143 patients. In our study, the sample group was formed by 84 patients, which is comparable with the numbers of the other studies.[7,8]

Considering the fact that more active lesions occurred in an age younger than 40 years (Figure 5), it could be assumed that younger patients possess a higher risk of recurrence. But seroprevalence of *T. gondii* infection increases with age showing highest rates of infection in adolescents and young adults.[29–35] Therefore, 80.4% of the cases became a manifest at an age younger than 40 years, with a mean age of 27.19 years (Figure 2). Concurring results of a mean age of 25.3 years and 26.5 years at the time of the first manifestation of OT were published by Friedmann and Knox[5] and Gilbert et al.[10] Bosch-Driessen et al[9] also described a mean age of 29.5 years and showed that, in 75% of the cases, OT became a manifest before the age of 35 years. Many more patients get infected with *T. gondii* at a younger age, concluding that the absolute number of new infections continues to decrease with increasing age. Nonetheless, recurrences especially occur at the beginning of an infection showing a decrease of the risk of recurrence with the duration of the disease (Figure 4). Therefore, age-related distribution of active lesions can be explained by the fact that more patients get infected at younger age. Consequently, the presence of a higher absolute number of active lesions at a younger age cannot lead to the conclusion that individuals at a younger age possess a higher risk of recurrence.[12]

Therefore, we set out to identify the influence of patient age at the time of the first active lesion on the risk of recurrence (Figure 6). Only data within the first 10 years of follow-up from patients with primary OT and a follow-up of >4 years were included. This measure is explained by the fact that using the variable mean number of recurrences/active lesions per year is only appropriate if there are comparable times of follow-up among study subjects.[15] An even more uniform follow-up than used in this study would have been desirable but could not be chosen because of a limited amount of patient data. To eliminate the confounding variable of nonuniform drug therapy at the time of the first active lesion, we subdivided the patients into groups regarding their treatment. It should be noted that clindamycin is used as the first line treatment of OT for >10 years at the Interdisciplinary Uveitis Center, University of Heidelberg (Table 2) because of showing less side effects than the most commonly used regimen pyrimethamine/sulfadiazine.[36,37] By eliminating all currently imaginable confounders, the influence of patient age at the time of the first active lesion on the risk of recurrence could be shown despite the limitation of a low number of patients (Figure 6). Thus, the risk of recurrence seems to be influenced by the patient's age at the time of the first active lesion. To confirm our result, a considerably larger number of patients would be desirable.

Because the risk of recurrence seems to be influenced by the patient's age at the time of the first active lesion, it seems plausible that the risk of recurrence after every active lesion in general is also influenced by the patient's age (Figure 7). Nonuniform drug therapy may also be a confounder in this analysis. Because medical treatment was retrospectively not determined for all active lesions, this confounder has to be specified in the following studies.

Concerning the influence of patient age on the risk of recurrence, one can summarize that older age at the time of the first active lesion and at the time of any active lesion seems to predispose for a higher risk of recurrence. Therefore, older patients could be treated with a secondary antibiotic prophylaxis after suffering an active lesion of OT.

Conclusion

The risk of recurrence can be influenced by many confounding variables. Thus, our study is the first in

the literature using only data of patients with primary OT when necessary, because precise date of the first active lesion could be determined only for these patients, and therefore the complete history of disease is known. In analyses using the variable mean number of recurrences/active lesions per year, data of study subjects were restricted to comparable times of follow-up as suggested by Holland et al.[15] As shown in Table 3, the drug therapy received subsequent to the first active lesion seems to be a confounder that influences the risk of recurrence. Therefore, patients with primary OT were subdivided into groups regarding their received drug therapy for analyzing the influence of patient age at the time of the first active lesion on the risk of recurrence. By restricting confounders in all this way, n is low in some analyses, but highly valid statistical results can be achieved because based on our current understanding of the disease, we are unaware of other confounding variables that may influence the risk of recurrence. Therefore, despite the limitations of a low n in some analyses and the retrospective nature of this study, our study clarifies the interval during which a secondary antibiotic prophylaxis could be justified and factors predisposing for a higher risk of recurrence in the best currently possible way. The only preferable alternative is a prospective study. However, concerning OT, such a study might be too complex, time-consuming, and costly.

To summarize, the risk of recurrence is highest directly after the most recent active lesion implying a decrease over the recurrence-free survival time; the risk of recurrence also decreases with the duration of the disease, and it is influenced by a patient's age at the time of the first active lesion and at the time of any active lesion. Thus, in our opinion, a secondary antibiotic prophylaxis should be considered 1) during the first year (optionally the first 2 years) after an active lesion has occurred, and 2) in patients of older age, especially if primarily infected with *T. gondii* in older age. This should be discussed with each patient individually, especially when the lesion is close to the macula.

Our study is of value when deciding about a secondary antibiotic prophylaxis for patients with a high risk of recurrence of OT. The study may therefore help to improve the quality of life and prevent vision loss in patients with recurring OT.

Key words: ocular toxoplasmosis, posterior uveitis, prognosis, recurrences, treatment, uveitis.

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