

Adverse Event Profile of Pyrimethamine-Based Therapy in Toxoplasmosis: A Systematic Review

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Published online: 6 September 2017

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Abstract

Introduction Approximately a third of the population worldwide is chronically infected with *Toxoplasma gondii*. Pyrimethamine-based regimens are recommended for the treatment of toxoplasmosis.

Objective The aim was to evaluate the safety profile of pyrimethamine-based treatment for the three main *Toxoplasma* manifestations: toxoplasmic encephalitis (TE), ocular toxoplasmosis, and congenital toxoplasmosis.

Methods PubMed, Cochrane Library, and Google Scholar databases were searched through August 1, 2016. Randomized, observational, prospective/retrospective, and cohort studies were eligible. Thirty-one studies were included with a total of 2975 patients. Of these, 13 were in congenital toxoplasmosis ($n = 929$), 11 in ocular toxoplasmosis ($n = 1284$), and seven in TE ($n = 687$). Across manifestations, adverse event (AE)-related treatment discontinuation and/or change in therapy involved $\leq 37\%$ of patients and occurred in $>55\%$ of studies: 100% for ocular toxoplasmosis, 57.1% for TE, and 61.5% for congenital toxoplasmosis. The most commonly observed AEs were bone marrow suppression, dermatologic, and gastrointestinal (GI). The prevalence of bone marrow suppression-related AEs was $\leq 50\%$ in congenital toxoplasmosis, $\leq 42.7\%$ in TE, and $\leq 9.0\%$ in ocular toxoplasmosis. The frequency of GI and dermatologic AEs were ≤ 100 and $\leq 11.1\%$, respectively, for ocular toxoplasmosis, ≤ 10.7 and $\leq 17.9\%$ for TE, and ≤ 10.8 and $\leq 2.1\%$ for congenital

toxoplasmosis. Steven–Johnson syndrome was reported in two patients with ocular toxoplasmosis and one with TE.

Conclusion The AE profile associated with pyrimethamine-based treatments differed by each manifestation of toxoplasmosis and within a given manifestation. Hematologic AEs occurred across all manifestations indicating the importance of monitoring the blood of patients administered pyrimethamine-based regimens.

Key Points

The types of adverse events associated with pyrimethamine-based treatment of toxoplasmosis differed across the three clinical manifestations of the disease: ocular toxoplasmosis, toxoplasmic encephalitis, and congenital toxoplasmosis.

The differences in adverse event profiles among the three manifestations and between studies within each manifestation are likely due to differences in patient populations, dosing regimens, study protocols, and pharmacokinetics of pyrimethamine.

Hematologic adverse events were observed across all manifestations, highlighting the importance of monitoring blood in patients receiving pyrimethamine plus other drugs to treat toxoplasmosis.

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1 Introduction

Toxoplasmosis is caused by the protozoan parasite *Toxoplasma gondii* (*T. gondii*), an obligate intracellular parasite capable of infecting a wide range of hosts and many different types of host cells [1]. Approximately a third of the population worldwide is chronically infected with *T. gondii* [2]. In the USA, it is estimated that about 22% of the population ≤ 12 years are infected with the parasite [3]. The seroprevalence of *T. gondii* varies across the world. For example, *T. gondii* seroprevalence is $>60\%$ in Brazil, the Philippines, and Madagascar; 40–60% in Egypt, Argentina, and several European countries, including France, Germany, and Poland; and 20–40% in Australia, Chile, Saudi Arabia, Iran, and the USA [4]. Infections occur through consuming food (including meat products) or water contaminated with cat feces, mother-to-child (congenital/vertical) and iatrogenic (transplanted organs and blood transfusion) transmission [3]. The three most important manifestations of *T. gondii* infection are toxoplasmic encephalitis (TE), ocular toxoplasmosis, and congenital toxoplasmosis [3, 5, 6]. Benign lymphadenopathy is also observed in immunocompetent individuals and often resolves without therapy [3]. Each year in the USA an estimated 4839 persons develop symptomatic ocular toxoplasmosis [7], an average of 20,258 hospitalizations are associated with TE [8], and an estimated one in 10,000 live births has congenital toxoplasmosis [9].

The recommended first-line treatment for toxoplasmosis is a combination therapy based on pyrimethamine, sulfadiazine, and leucovorin or folinic acid [3, 10]. Pyrimethamine is an anti-parasitic medication that has been available for over 60 years and is indicated for the treatment of toxoplasmosis. Pyrimethamine and sulfadiazine are thought to act synergistically to treat toxoplasmosis by inhibiting *T. gondii* proliferation and survival through inhibiting the folate metabolic pathway [3, 10–12]. The drugs inhibit dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS), respectively, and consequently block the synthesis of tetrahydrofolate, which is required by the parasite for DNA synthesis [12, 13]. Pyrimethamine-associated adverse events (AEs) are mainly related to its inhibition of folic acid metabolism in tissues with high metabolic activity (e.g., epithelium and bone marrow) [14]. Pyrimethamine-related bone marrow suppression is reversible and usually recovers following cessation or reduction of therapy and/or addition of folinic acid or leucovorin [15, 16]. Leucovorin and folinic acid are reduced forms of folic acid and are readily converted to tetrahydrofolate [17], hence, bypassing the inhibition of DHFR by pyrimethamine.

AEs associated with pyrimethamine often result in change or discontinuation of therapy, and consequently impact treatment outcomes. To date, several systematic reviews have focused on the efficacy and safety of different treatment regimens in treating TE in adults with HIV or AIDS [18–21], congenital toxoplasmosis [18], and ocular toxoplasmosis [18, 22]. However, none have assessed the overall safety of pyrimethamine-based treatment regimens across all three major manifestations. The purpose of this systematic review is to provide a comprehensive summary of the safety of pyrimethamine-based therapy in treating TE, ocular toxoplasmosis, and congenital toxoplasmosis. Due to the small number of randomized trials in toxoplasmosis, relative to the number of studies with other designs, our analysis allowed for inclusion of studies of varying design, such as single-arm, observational cohorts, randomized, and retrospective studies.

2 Methods

2.1 Search Strategy

The review was performed in accordance with PRISMA guidelines. PubMed, Google Scholar, and Cochrane databases were searched through August 1, 2017 using the following search terms: pyrimethamine, Daraprim, Fansidar, Metakelfin, Fansimef, 5-(4-chlorophenyl)-6-ethyl-2,4-pyrimidinediamine, encephalitis, cerebral, toxoplasmosis, toxoplasmic, congenital, and *gondii*. A manual search of references from recent reviews and relevant published original studies was also performed to identify additional studies. Studies eligible for inclusion were randomized, observational prospective and retrospective, and cohort studies. Included studies reported AEs for pyrimethamine-based treatment regimens, had patient populations of ten or more, and were published in English in peer-reviewed journals. For TE, only studies performed from 1996 to August 1, 2017 (independent of publication date) were included. The decision to review only TE papers performed during this time period was based on the introduction of highly active antiretroviral therapy (HAART), which in 1996 became widely available, resulting in a dramatic decrease in mortality among patients with AIDS; mortality declined from 29.4 per 100 person-years in 1995 to 8.8 per 100 person-years in the second quarter of 1997 [23]. Several papers have indicated that toxoplasmosis treatment response in patients with HIV/AIDS and TE, such as relapse rate, differed between the pre-HAART and post-HAART periods [24–26]. In addition, HAART is currently the standard of care for the treatment of HIV/AIDS and, hence, the AE profiles reported following 1996 for this patient population

are clinically most relevant. Letters, comments, editorials, proceedings, case reports, correspondence, personal communications, in vitro studies, and preclinical studies were excluded. Study eligibility and data extraction were performed by two independent reviewers, and a third reviewer was consulted to adjudicate disagreements.

2.2 Data Extraction and Quality Assessment

The following information was extracted: first author, age, gender, treatment regimens, duration of treatment, duration of follow-up, and AEs. AEs are those that were observed following treatment and, depending upon the study, were reported as AEs, safety, side effects, and/or toxicities.

The quality of the included studies was evaluated using the National Heart, Lung, and Blood Institute of the National Institutes of Health Study Quality Assessment Tools for observational cohort and cross-sectional studies, before–after (pre–post) studies with no control group, and controlled intervention studies [27]. Each report was rated as poor, fair, or high quality.

3 Results

3.1 Search Results

The search identified 2504 records, and an additional 174 records were identified through other sources (Fig. 1). Of

the 2678 records initially identified, 2385 were excluded after removal of duplicates and initial title and abstract screening. Following a full-text review, 262 additional studies were excluded for being case reports, evaluating only drug stability, not reporting safety, describing only a study protocol, not presenting efficacy of a pyrimethamine-based regimen, duplication of another publication, being a TE study performed prior to 1996 (see Sect. 2.1, for explanation for including only post-1996 studies), or being a survey. Thirty-one studies were included in the systematic review. The number of studies for each major manifestation were 13 for congenital toxoplasmosis, 11 for ocular toxoplasmosis, and seven for TE. The number of patients totaled 2975.

3.2 Quality Assessment

The majority of included studies obtained quality scores of medium to low due to high risk of bias with no blinding of participants, personnel, and outcome assessment being the main issues.

3.3 Summary of Adverse Events in Ocular Toxoplasmosis

The search identified 11 studies that reported AEs associated with pyrimethamine-based treatment in ocular toxoplasmosis (Table 1). The 11 studies included a total of 1284 patients (range 19–303), of which 870 received a

Fig. 1 Search flow diagram

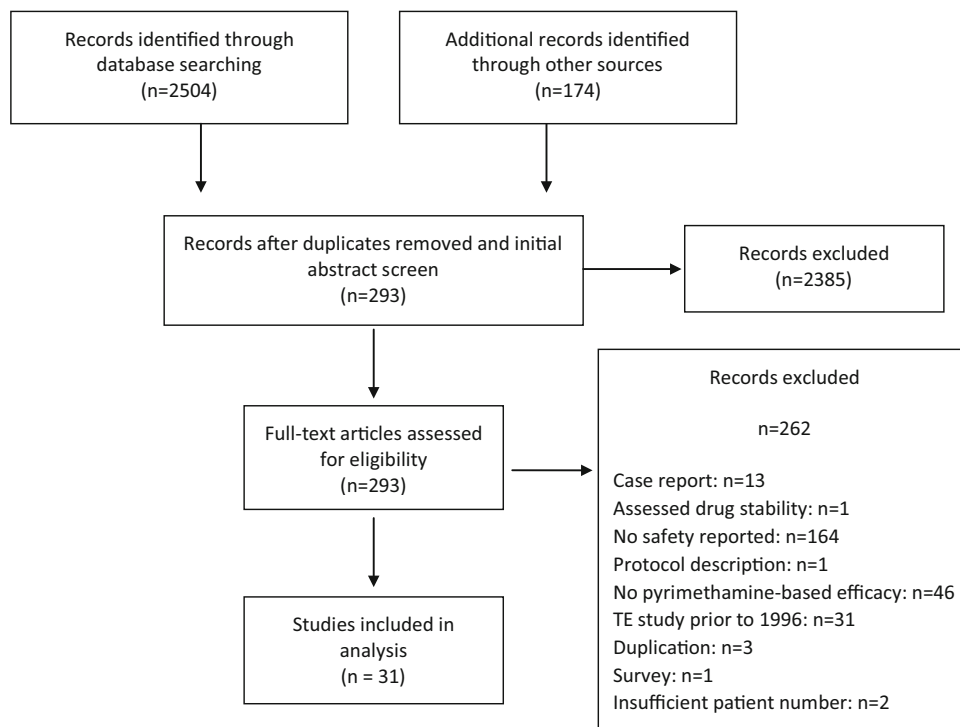


Table 1 Characteristics of included ocular toxoplasmosis studies

Study (first author, year)	Study design	Study population	Patient number	Demographics	Treatment	Follow-up (months)
Randomized studies						
Acers (1964) [28]	Prospective, randomized, double-blind	Presumptive diagnosis of toxoplasmic retinochoroiditis	20	Age (range) 18–49 years Male 45%	PTri (<i>n</i> = 10): PYR (200 mg 1st day, 100 mg 2nd day, 50 mg on days 3–15, 25 mg from day 16–56) plus trisulfapyrimidines (2 g/day) for 8 weeks plus Pred (40 mg/day for 7 days followed by 20 mg/day for the next 7 weeks) Deltasone (<i>n</i> = 10): Pred (40 mg/day for 7 days followed by 20 mg/day for 7 weeks)	24
Baharivand (2013) [29]	Prospective, randomized, single-blind	Toxoplasmic retinochoroiditis	66	Mean age 27 years Male 41%	IVCD (<i>n</i> = 32): CLJ (1 mg intravitreal injection) plus DXM 400 µg PS (<i>n</i> = 34): PYR (75 mg/day for 2 days followed by 25 mg/day) plus SDZ (2 g/day for 2 days followed by 1 g QID) plus folic acid (5 mg/day) for 6 weeks. Pred (50 mg/day) for 3 weeks starting 3rd day of therapy	24
Balaskas (2012) [30]	Prospective, randomized	Non-vision-threatening toxoplasmic retinochoroiditis	19	Mean age 48 years Male 44%	AZM (<i>n</i> = 10): AZM (500 mg QD) plus Pred (1 mg/kg/day initiated 3 days after start of therapy tapering off by 5 mg every 3 days) PS (<i>n</i> = 9): PYR (25 mg BID) plus SDZ (<65 kg received 1000 mg TID, or >65 kg received 1000 mg QID) plus folic acid (15 mg QID). Pred (1 mg/kg/day) initiated 3 days after start of therapy tapering off to 5 mg every 3 days	>3
Bosch-Driessen (2002) [31]	Prospective, randomized, open-label	Sight-threatening ocular toxoplasmosis	46	Age between 16 and 80 years Gender NR	Treatment was discontinued as soon as disease was deemed inactive based on clinical evaluation. Mean time to treatment discontinuations was 73 days for AZM and 49 days for PS PYR + AZM (<i>n</i> = 24): PYR (100 mg day 1, followed by 50 mg/day) plus AZM (250 mg/day [<i>n</i> = 7] or 500 mg every other day [<i>n</i> = 17]) plus folic acid (15 mg/day). Pred (40 mg) from day 3–10 PS (<i>n</i> = 22): PYR (100 mg/day 1, followed by 50 mg/day) plus SDZ (4000 mg/day) plus folic acid (15 mg/day). Pred (40 mg) from day 3–10 Treatment was given for at least 4 weeks	15

Table 1 continued

Study (first author, year)	Study design	Study population	Patient number	Demographics	Treatment	Follow-up (months)
Rothova (1993) [32]	Prospective, randomized	Ocular toxoplasmosis	149	Mean age 27 years Male 54%	PS (<i>n</i> = 35): PYR (100 mg the first day followed by 50 mg/day) plus SDZ (4 g/day) plus folinic acid (5 mg twice a week) CS (<i>n</i> = 46): CLI (300 mg QID) plus SDZ (4 g/day) TMP-SMX (<i>n</i> = 27): TMP-SMX (960 mg BID during the first 2 weeks, then 380 mg BID) Untreated (<i>n</i> = 41): Treatment given for at least 4 weeks All arms received 60 mg/day corticosteroids from day 3–7, thereafter gradually tapered	36
Soheilian (2005) [33]	Prospective, randomized, single-blind	Ocular toxoplasmosis	59	Mean age 23.5 years Male 60%	PS (<i>n</i> = 20): PYR (100 mg daily for 2 days, followed by 25 mg daily) plus SDZ (2 g daily for 2 days, followed by 500 mg QID) plus folinic acid (5 mg daily) TMP-SMX (<i>n</i> = 30): TMP (80 mg BID) plus SMX (400 mg BID) In both arms, treatment was continued for 6 weeks Both arms received Pred (1 mg/kg/ daily) on day 3, which was tapered over 2 weeks	33
Soheilian (2011) [34]	Prospective, randomized, single-blind	Ocular toxoplasmosis	68	Mean age 23.3 years Male 53%	CLI + DXM (IVCD) (<i>n</i> = 34): CLI (1–3 intravitreal injections of 1 mg) plus DXM (1–3 intravitreal injections of 400 µg) PS (<i>n</i> = 34): PYR (75 mg daily for 2 days followed by 25 mg daily) plus SDZ (4 g daily for 2 days followed by 500 mg BID) plus folinic acid (5 mg/day) for 6 weeks. Pred 1 mg/kg daily for 3 weeks starting day 3	24
Observational studies						
Cananuncio (1963) [35]	Prospective, cohort	Active endogenous uveitis	106	NR	SPY (<i>n</i> = 60): SPY (option 1) 6 g day 1 BID, then 1 g QD, or (option 2) 2 g day 1 single dose for an average of 6 weeks PYR + SND (<i>n</i> = 45): PYR (initial dose of 200 mg with daily decreases of 25 mg until a maintenance dosage of 25 mg a day was reached. A sulfonamide was also administered Treatment for both arms was for approximately 6 weeks	28

Table 1 continued

Study (first author, year)	Study design	Study population	Patient number	Demographics	Treatment	Follow-up (months)
Lam (1993) [36]	Retrospective, chart review	Active toxoplasmic lesion	150	Mean age 34.2 years Female 56%	Quadruple therapy ($n = 36$): PYR (loading dose 75 mg, then 25 mg daily) plus trisulfapyrimidines (SDZ may be substituted) (loading dose 2 g, then 1 g QID) plus CLI (300 mg QID) plus Pred (60–80 mg every other day) PYR therapy was continued for up to 2 weeks. Oral Pred was tapered (40–60 mg every other day in 2nd week, then 20–40 mg every other day in the 3rd week) Other therapy ($n = 11$): CLI alone, sulfadiazine alone, PYR and trisulfapyrimidines, and minocycline alone Untreated ($n = 103$)	186
Borkowski (2016) [37]	Retrospective, chart review	Toxoplasmic retinochoroiditis	564	Age 30.3 years Female 61.1%	Phase 1 (acute): PYR + SDX ($n = 564$): PYR 50-mg and SDX 1000-mg loading dose for first 2 days, followed by PYR 25 mg plus SDX 500 mg daily on days 3–21 SPY 3 million IU thrice daily from day 2–12 followed by AZM 500 mg/day for 6 days Phase 2 (maintenance) [51]: PYR + SDX ($n = 303$): PYR 25 mg plus SDX 500 mg twice weekly for 6 months	120
Hellenstein 2017 [38]	Retrospective chart review	Ocular toxoplasmosis	37	Age 37 years Female 44.9%	PS ($n = 37$): PYR (loading dose 75 mg/day for 3 days, then 50 mg/day) plus SDX (4 g/day) plus calcium folinate (15 mg twice weekly) plus corticosteroid (0.5–1 mg/kg)	9

AZM azithromycin, BID twice daily, CLI clindamycin, CS clindamycin plus sulfadiazine, DXM dexamethasone, IVCD intravitreal injected clindamycin plus dexamethasone, NR not reported, Pred prednisone, PS pyrimethamine plus sulfadiazine, PTri pyrimethamine plus trisulfapyrimidine, PYR pyrimethamine, QID 4 times per day, SDX sulfadoxine, SDZ sulfadiazine, SND sulfonamide, SPY spiramycin, TID 3 times per day, TMP-SMX trimethoprim and sulfamethoxazole

Table 2 Adverse events of pyrimethamine-based therapies for included studies in ocular toxoplasmosis

Study (first author, year)	PYR-based treatment	Total AEs	Discontinuation/change of treatment	Hematologic		GI	Dermatologic		Other
				Thrombocytopenia	Leukopenia		Skin rash	Pruritus	
Randomized studies									
Acers (1964) [28]	PTri	3/10 (30%)	<i>Discontinued:</i> 1/10 (10%) (due to platelet drop/removed from study)	1/10 (10%)	-	-	-	-	3/10 (30%) (nausea, loss of appetite, mild urticaria, arthralgia)
Baharivand (2013) [29]	PS	1/34 (2.9%)	<i>TX change:</i> 1/34 (2.9%) (changed to AZM)	-	-	-	-	-	Hepatotoxicity: 1/34 (2.9%)
Balaskas (2012) [30]	PS	9/9 (100%)	<i>TX change:</i> 1/9 (11.1%) (due to skin rash/treatment discontinuation)	-	-	9/9 (100%) (GI disorder unspecified)	1/9 (11%)	-	Malaise, dizziness, headache
Bosch-Driessen (2002) [31]	PYR + AZM PS	PYR + AZM: 8/24 (33%) PS: 14/22 (64%)	<i>Discontinued:</i> PS: 3/22 (14%) (stenocardia; severe GI and emotional distress; skin rash) PYR + AZM: 0/24 (0%)	PS: 2/22 (9%) PYR + AZM: 0/24 (0%)	-	PS: 1/24 (4.2%) PYR + AZM: 1/22 (4.5%)	PS: 1/22 (4.5%) PYR + AZM: 0/24 (0%)	PS: 1/22 (4.5%) PYR + AZM: 1/24 (4.2%)	PYR + AZM: Increased liver enzymes: 2/24 (8.3%) Increased creatinine levels: 3/24 (13%) Other: 1/24 (4.0%) ^a
Rothova (1993) [32]	PS	-	<i>Discontinued:</i> PS: 9/35 (26%) (due to thrombocytopenia, leukopenia)	-	-	-	-	-	PS: Malaise: 5/22 (23.0%) Increased serum liver enzymes: 1/22 (5.0%) Increased serum creatinine: 1/22 (5.0%) Other: 2/22 (9.0%) ^a
Soheilian (2005) [33]	PS	1/29 (3.4%)	<i>Discontinued:</i> 1/29 (3.4%) (due to rash)	-	-	-	1/29 (2.9%)	-	-

Table 2 continued

Study (first author, year)	PYR-based treatment	Total AEs	Discontinuation/change of treatment	Hematologic		GI		Dermatologic		Other
				Thrombocytopenia	Leukopenia	Diarrhea	Skin rash	Pruritus	Steven-Johnson syndrome	
Soheilian (2011) [34]	PS	2/36 (5.6%)	<i>Discontinued:</i> 2/36 (5.6%) (due to skin rash and thrombocytopenia)	1/36 (2.8%)	-	-	1/36 (2.8%)	-	-	-
Observational studies										
Canamucio (1963) [35]	PYR + SND	9/45 (20%)	<i>Discontinued:</i> 9/45 (20%) (leukopenia, thrombocytopenia, agranulocytosis, hemoglobin depression, epistaxis)	-	-	-	-	-	-	Agranulocytosis; hemoglobin depression; epistaxis, leukopenia, thrombocytopenia
Retrospective studies										
Lam (1993) [36]	PTri + CLI	4/36 (11.1%)	-	-	-	-	4/36 (11.1%)	-	-	-
Borkowski (2016) [37]	PYR + SDX Phase 1 (acute) Phase 2 (maintenance)	Phase 2: 13/564 (2.3%)	<i>Discontinued:</i> Phase 1: 12/564 (2.2%) Phase 2: 7/564 (2.3%)	Phase 1: 47/564 (8.3%)	-	-	Phase 1: 17/564 (3.0%)	-	Phase 1: 2/564 (0.4%)	Phase 1: Abdominal pain: 8/564 (1.4%) Increased serum liver enzymes (>30%): 139/564 (24.6%) Elevated creatinine (5.4%) Elevated liver enzymes (5.4%) Vomiting (5.4%) Facial swelling (2.7%)
Helfenstein (2017) [38]	PS	9/37 (24.3%)	<i>Discontinued:</i> 9/37 (24.3%)	-	-	-	2/37 (5.4%)	-	-	-

AEs adverse events, AZM azithromycin, CLI clindamycin, GI gastrointestinal, PTri pyrimethamine plus trisulfapyrimidine, PS pyrimethamine plus sulfadiazine, PYR pyrimethamine, SDX sulfadoxine, SND sulfonamide, TX treatment

^a Palpitations, stenocardia reversible aphasia

treatment regimen containing pyrimethamine. None of the patients were immunocompromised. Seven studies were randomized prospective studies, which compared at least two different treatment regimens [28–34], one study was a prospective cohort study [35], and three were retrospective chart reviews [36–38] in design. All studies included pyrimethamine-based regimens that contained a sulfonamide, except for the study of Bosch-Driessen et al. [31], which contained one treatment arm with pyrimethamine plus azithromycin. Ocular toxoplasmosis was diagnosed both by clinical (e.g., presence of vitreous inflammation, retinochoroiditis, retinal scars) and serologic analyses of the presence of anti-*Toxoplasma* antibodies (IgG and IgM).

The dose of pyrimethamine varied across studies. Four studies did not report coadministering folinic acid or leucovorin with pyrimethamine [28, 35–37]. Ten of the studies first administered a loading dose of pyrimethamine ranging from 50 to 200 mg/day [29, 31–38]. Other treatment regimens evaluated were spiramycin, clindamycin, azithromycin, and trimethoprim-sulfamethoxazole (TMP-SMX). Duration of acute treatment varied among studies, ranging from 2 to about 10 weeks. The range of follow-up among the studies was from <3 months to 16 years.

The total number of patients reporting AEs varied across studies, ranging from 2.3 to 100% (Table 2). Each of the 11 studies reported discontinuation or change in treatment due to AEs (range 0–26%).

Hematologic AEs indicative of bone marrow suppression were reported in five (45.5%) of the 11 studies [28, 34, 35, 37, 39], and included patients with thrombocytopenia ($n = 52$). Leukopenia and agranulocytosis were listed as toxic reactions in one study [35]. No neutropenia was reported. Prevalence of these AEs reported among the studies ranged from 2.8 to 10.0%.

A number of non-hematologic AEs were reported across studies. Gastrointestinal (GI)-related AEs were reported in four studies [28, 31, 37, 38], and included diarrhea, GI distress, nausea, vomiting, and loss of appetite. Eight studies (72.7%) reported dermatologic AEs [28, 30, 31, 33, 34, 36–38], including skin rash, pruritus, and Steven–Johnson syndrome. The most common dermatologic AE was skin rash (range 2.8–11%), the presence of which was only associated with pyrimethamine plus sulfadiazine treatment. Two patients (2/564; 0.4%) in one study developed Steven–Johnson syndrome and discontinued therapy [37]. The outcomes of these patients are unclear, as the information is not described in the paper.

Altered liver function, including increased liver enzymes, was reported in four studies (36.4%) [29, 31, 37, 38], with a frequency that ranged from 2.9 to 24.6%, and studies reported increased serum creatinine levels (range 45–13%) [31, 38]. Other AEs observed in single studies included fever, epistaxis, dizziness,

headache, reversible aphasia, palpitations, stenocardia, emotional distress, arthralgia, facial swelling, and malaise. The prevalence of these AEs, where reported, was $\leq 10\%$ except for malaise, which was reported in one study to have a prevalence of 23% [31].

3.4 Summary of Adverse Events in Toxoplasmic Encephalitis

The search identified seven studies that were performed from 1996 to August 1, 2017 (post-HAART) that reported AEs associated with pyrimethamine-based treatment of TE (Table 3). The seven studies included a total of 687 patients (range 11–323), of which 626 received a treatment regimen containing pyrimethamine for acute and/or maintenance therapy for TE. Two of the studies were randomized [40, 41], one was prospective [42], and four were retrospective [43–46] in design. The patient population in all studies consisted of patients with TE and with HIV infection or AIDS. Acute therapy was evaluated in six studies [40, 42–46] and maintenance treatment in four [40, 41, 45, 46]. The pyrimethamine-based treatment regimens among the studies were heterogeneous. The most common regimen evaluated was pyrimethamine plus sulfadiazine ($n = 3$). Other pyrimethamine-based regimens included atovaquone, TMP-SMX, or sulfadoxine or another sulfonamide. Only two studies did not report coadministering folinic acid or leucovorin [42, 46]. Acute treatment ranged from 2 to 9 weeks. The duration of follow-up, when reported, varied and ranged from 4 to 48 weeks.

Across the studies, the range of total AEs was from 0 to 62.5% (Table 4). Treatment discontinuation due to AEs ranged from 10.6 to 18.9%. AEs observed in two or more studies included those associated with bone marrow suppression, GI disturbance, rash, and fever (Table 4). Three studies reported rash (range 6.3–10.8%) [41, 43, 45], two reported nausea and/or vomiting (range 3.4–10.7%) [40, 41], and two reported fever (range 7.6–10.7%) [40, 41]. Hematologic AEs that occurred in two or more of the seven studies included neutropenia ($n = 2$) [40, 45], thrombocytopenia ($n = 2$) [40, 43], and pancytopenia ($n = 2$) [43, 46]. Among these studies, the frequency of neutropenia ranged from 7.0 to 25%, thrombocytopenia from 7.1 to 32.5%, and pancytopenia from 6.6 to 21.7%. Other AEs associated with bone marrow suppression reported in a single study were leukopenia (75/323; 23.2%) [43], anemia (138/323; 42.7%) [43], hematologic toxicity (2/66; 3.0%) [41], bleeding (57/323; 17.6%) [43], and thrombocytopenia with major bleeding (4/16; 25%) [45].

Non-hematologic AEs reported in single studies included eczema (19/106; 17.9%) [46], Steven–Johnson syndrome (1/16; 6.3%) [45], pain or discomfort (2/28; 7.1%)

Table 3 Characteristics of included toxoplasmic encephalitis studies

Study (first author, year)	Study design	Study population	Patient number	Demographics age (mean)	Treatment	Follow-up (weeks)
Randomized studies						
Chirgwin (2002) [40]	Open-label, randomized, phase 2	Definitive histologically proven diagnosis of TE or presumptive TE based upon compatible clinical and radiologic findings, either acute or relapsed, and serologically positive for HIV or a diagnosis of AIDS	39	Age 35 years Males 79%	<i>Acute:</i> 6 weeks: ATO + PYR (<i>n</i> = 28): ATO (1500 mg BID) plus PYR (200-mg loading dose, followed by 75 mg/day, or if <60 kg 50 mg/day) plus LEU 10 mg daily ATO + SDZ (<i>n</i> = 11): ATO (1500 mg BID) plus SDZ (1500 mg QID, or if <60 kg 1000mg QID) plus LEU 10 mg/day <i>Maintenance:</i> 42 weeks after acute treatment with same treatment regimen as acute therapy <i>Maintenance:</i> Daily PS (<i>n</i> = 58): PYR (25 mg/day) plus SDZ (1000 mg BID) plus folinic acid 15 mg/day Triweekly PS (<i>n</i> = 66): PYR (50 mg 3 times a week) plus SDZ (1000 mg BID) plus folinic acid (15 mg 3 times a week)	48
Podzamczar (2000) [41]	Open-label, randomized, multicenter	HIV-infected patients after resolution of an acute episode of TE that was treated with SDZ (1 g QID) plus PYR (50 mg/day) and folinic acid (15 mg/day) for 4–8 weeks	124	Daily PS: Age 35.7 years Male/female ratio 3.5 Triweekly PS: Age 34.9 years Male/female ratio 5.0		44 (median) 12
Observational studies						
Chaddha (1999) [42]	Prospective, open-label	HIV-1 or who belonged to a group at high risk for HIV-1 infection and who also had a neuroradiographic abnormality compatible with diagnosis of TE	11	Age 32 years Males 91%	<i>Acute:</i> 6 weeks: PYR + TMP-SMX: PYR (200-mg loading dose, followed by 75 mg per day) plus SMX (100mg/kg) plus TMP (20 mg/kg) in 4 divided doses per day	24
Amogne (2006) [43]	Retrospective	AIDS who were consecutively admitted due to presumed TE	323	Age 34 years Males 50%	Acute (≥ 2 weeks): PYR + SDX: PYR (100 mg or 25–50 mg for 2 days, followed by 25 mg/day) plus SDX (500 mg) plus folinic acid	4 (median)
Arens (2007) [44]	Retrospective	HIV-infected patients diagnosed with TE at discharge	43	Age 34 years Males 50%	<i>Acute:</i> PS (<i>n</i> = 18): (specific dosing not reported) plus folinic acid TMP-SMX (<i>n</i> = 25): (specific dosing not reported)	NR

Table 3 continued

Study (first author, year)	Study design	Study population	Patient number	Demographics age (mean)	Treatment	Follow-up (weeks)
Goswami (2015) [45]	Retrospective	AIDS with a first episode of TE	41	Age 29.81 years Male 88%	<i>Acute (4–6 weeks):</i> PS (<i>n</i> = 16): PYR (200-mg loading dose, followed by 50 mg/day for <60 kg body weight or 75 mg/day based for >60 kg body weight) plus SDZ (4 g QID) plus folic acid (15 mg 4 times a week) TMP-SMX + CLI (<i>n</i> = 25): TMP 20 mg/kg/day plus SMX (fixed ratio of 1:5) plus CLI (600 mg TID) <i>Maintenance:</i> PS: PYR (25mg/day) plus SDZ (500 mg QID) TMP-SMX + CLI: TMP-SMX (1 double strength tablet BID) plus CLI (300 TID)	NR
Arendt (1999) [46]	Retrospective	AIDS who also had TE or PCP	106	Age 40.4 years Males 95%	<i>Acute (2–9 weeks):</i> PYR + SND + CLI: PYR (75 mg/day) plus sulfonamides (2 g/day) or clindamycin (2400 mg/day IV) <i>Maintenance:</i> PYR (75 mg/day)	NR

AIDS acquired immunodeficiency syndrome, *ATO* atovaquone, *BID* twice daily, *CLI* clindamycin, *HIV-1* human immunodeficiency virus-1, *IV* intravenous, *LEU* leucovorin, *NR* not reported, *PCP* pneumocystis carinii pneumonia, *PS* pyrimethamine plus sulfadiazine, *PYR* pyrimethamine, *QID* 4 times per day, *SDX* sulfadoxine, *SDZ* sulfadiazine, *SND* sulfonamide, *TE* toxoplasmosis encephalitis, *TID* 3 times per day, *TMP-SMX* trimethoprim plus sulfamethoxazole

Table 4 Adverse events of pyrimethamine-based therapies in toxoplasmic encephalitis in two or more studies

Study (first author, year)	PYR-based treatment	Treatment discontinued/change	Total AEs	Hematologic		GI		Dermatologic		Other
				Neutropenia	Thrombocytopenia	Pancytopenia	Nausea and/or vomiting	Rash		
Randomized studies										
Chirgwin (2002) [40]	PYR + ATO	9/28 (32%)	–	2/28 (7.1%)	2/28 (7.1%)	–	3/28 (10.7%)	–	–	AST or ALT levels >5 times ULN 9/28 (31.0%) Alkaline phosphatase level >5 times ULN 3/28 (10.7%) Pancreatic enzyme levels >2 times ULN 6/28 (21.4%) Fever 3/28 (10.7%) Pain/discomfort 2/28 (7.1%) Fever 5/58 (8.6%) Fever 5/66 (7.6%)
Podzamczar (2000) [41]	PS (daily)	7/58 (12.1%)	7/58 (12.0%)	–	–	–	2/58 (3.4%)	5/58 (8.6%)	–	
Prospective and retrospective studies										
Chaddha (1999) [42]	PYR + TMP-SMX	–	0%	–	–	–	–	–	–	–
Amogne (2006) [43]	PYR + SDX	68/323 (21.1%)	–	105/323 (32.5%)	70/323 (21.7%)	–	–	35/323 (10.8%)	–	Anemia 138/323 (42.7%) Leukopenia 75/323 (23.2%) Bleeding 57/323 (17.6%) Renal dysfunction 3/18 (17%) Liver impairment 2/18 (11%) Thrombocytopenia with major bleeding 4/16 (25%) Stevens–Johnson syndrome 1/16 (6.3%)
Arens (2007) [44]	PS	–	4/18 (22.2%)	–	–	–	–	–	–	–
Goswami (2015) [45]	PS	–	10/16 (62.5%)	4/16 (25.0%)	–	–	–	1/16 (6.3%)	–	Thrombocytopenia with major bleeding 4/16 (25%) Stevens–Johnson syndrome 1/16 (6.3%)
Arendt (1999) [46]	PYR + SND (acute) PYR (maintenance)	20/106 (18.9%)	–	–	–	–	–	–	–	Eczema 19/106 (17.9%) Renal failure 6/106 (5.7%)

AEs adverse events, ALT alanine transaminase, AST aspartate transaminase, ATO atovaquone, ATG gastrointestinal, PS pyrimethamine plus sulfadiazine, PYR pyrimethamine, SVD sulfonamide, TMP-SMX trimethoprim plus sulfamethoxazole, ULN upper limit of normal

Table 5 Characteristics of included congenital toxoplasmosis studies

Study (first author, year)	Study design	Study population	Patient number	Demographics	Treatment	Follow-up (months)
Randomized studies						
McLeod (2006) [47]	Randomized, longitudinal	Congenital toxoplasmosis in infants <2.5 months at diagnosis	120 infants	Mean age 10.5 years Male 55%	Infants: Pyr (1 mg/kg/day for either 2 [TX-A] or 6 months [TX-B]), then same treatment administered Mon, Wed, and Fri for remainder of the year) plus SDZ (100 mg/kg/day divided in 2 doses for 12 months) and leucovorin for 12 months	240
Observational studies						
Faucher (2012) [51]	Prospective, observational	Mothers infected with <i>T. gondii</i> and infants with a diagnosis of congenital toxoplasmosis	127 infants	Male 50%	Maternal: Infections >30 weeks of gestational age: PYR (1 g and SDX 50 mg every 10 days plus folinic acid 50 mg). For infections <30 weeks, SPY 9 million SI units/day until delivery. If seroconversion confirmed, switched to PYR plus SDX Infants: PYR (1.25 mg/kg) and SDX (25 mg/kg) every week plus folinic acid (50 mg every week) for 1 year	60
Guerina (1994) [48]	Prospective	Infants with congenital toxoplasmosis	49 infants	Gender and age NR	Infants: PYR (1 mg/kg/day for 3 days then every other day or 1/mg/kg/day for 6 months, then every other day for a year) plus SDZ (or triple sulfonamides) (100 mg/kg in 2 divided dose each day) and leucovorin (5–10 mg 3 times per week [dose increase with PYR toxicity])	12
Hohlfeld (1989) [52]	Prospective, longitudinal	Infants and mothers with <i>T. gondii</i> infection	52 pregnancies 54 infants	NR	Maternal: SPY 3 g/day throughout pregnancy from time of infection or until seroconversion. If seroconversion occurred, 3-week course PYR 50 mg, SDZ 3 gm/day alternating with 3 weeks of daily SPY (n = 37), or PYR 75 mg and SDX 1500 mg every 10 days (n = 6) until end of pregnancy. Folinic acid was also given Infants: PYR (2–5 courses of 0.50–0.75 mg/kg/day) and sulfonamides alternating with SPY 50 mg/kg/day for 1 year (n = 47) as described in Couvreur et al. [66]. SPY only (n = 7)	Infants 19
Lipka (2011) [49]	Prospective, longitudinal, PK	Infants treated for congenital toxoplasmosis	24 infants	Age 1–5 months Male 58%	Infants: PYR (0.5–1.0 mg/kg/day) plus SDZ (50–100 mg/kg/day in divided doses of 2–3 times/day for 2–6 months) followed by Fansidar (PYR + SDX) to end of year or longer. Folinic acid (7.5 mg twice a week)	36

Table 5 continued

Study (first author, year)	Study design	Study population	Patient number	Demographics	Treatment	Follow-up (months)
Mombro (1995) [53]	Prospective longitudinal	Infants with certain or probable congenital toxoplasmosis	77 infants	Newborns Gender NR	Infants: Prior to confirmation of <i>T. gondii</i> infection, SPY (50–100 mg/kg/day in 2 doses, repeated in 20-day cycles). If infection highly probable, PYR (20 mg) plus SMP (500 mg/20 kg every 10 days) in asymptomatic subjects; if symptomatic, PYR (20 mg) plus SMP (500 mg/10 kg every 7 days). Folic acid (4 mg/day) was also given. Treatment for 12–18 months	120
Schmidt (2006) [50]	Prospective, observational	Children with congenital toxoplasmosis	48 infants	Average age 32 days	Infants: PYR (2 mg/kg on the first day then 1 mg/kg/day) plus SDZ (50–100 mg/kg/day) plus folic acid (7.5 mg twice a week for 3 months). Addition of prednisolone was recommended in cases of active CNS involvement or retinochoroiditis	12
Stray-Pedersen (1980) [54]	Prospective, longitudinal	Children with congenital toxoplasmosis	52 infants/children	Newborns during their first year	Infants: PYR (1 mg/kg/day) plus SDZ (50 mg/kg/day) plus folic acid (0.1 mg/kg/day) for 3 weeks. The 3-week course was repeated twice during first year of life	36
Hotop (2012) [56]	Prospective	Toxoplasmosis acquired during pregnancy Newborns with toxoplasmosis	685 women 33 children	Pregnant women with serologic evidence of primary infection Newborns with serologic evidence of <i>T. gondii</i> infection	Maternal: Up to 16th week of gestation, SPY (3 million IU TID) followed by PYR (50 mg on day 1, thereafter 25 mg/day) plus SDZ (<80 kg, 3 g/day, ≥80 kg, 4 g/day) plus folic acid (10–15 mg/week) for 4 weeks. This treatment was extended up to 6 weeks when maternal infection occurred after the 16th week of pregnancy; up to the beginning of the 36th week of pregnancy if polymerase chain reaction of amniotic infection was positive; or until delivery when clinical manifestations were observed in utero Infants: PYR (1 mg/kg/day) plus SDZ (50 mg/kg/day) plus folic acid (2–3 mg/week) for 3 months for asymptomatic newborns; newborns with discrete symptoms received the same treatment but with higher dosage of SDZ (100 mg/kg body weight/day)	24

Table 5 continued

Study (first author, year)	Study design	Study population	Patient number	Demographics	Treatment	Follow-up (months)
Villena (1998) [55]	Prospective	Infants with congenital toxoplasmosis	Newborns with serologic evidence of <i>T. gondii</i> infection	78	Maternal: SPY (9 MU/day) from seroconversion until delivery. If positive prenatal diagnosis was made, mothers received PYR (1.25 mg/kg/15 days) plus SDX (25 mg/kg/15 days) plus folic acid (50 mg/15 days) Infants: Group 1 (n = 47): SDX (500 mg) plus PYR (25 mg) every 3rd month plus SPY (100 mg/kg/day) for 12 months Group 2 (n = 19): SDX (500 mg) plus PYR (25 mg) for 24 months Group 3: (n = 12): SDX (500 mg) plus PYR (25 mg) plus folic acid in the prenatal period and for 24 months post-birth	204
Teil (2016) [58]	Retrospective	Children with congenital toxoplasmosis	Neonates with confirmed congenital toxoplasmosis	65	Infants: PYR (3 mg/kg every 3 days) plus SDZ (25 mg/kg TID) and folic acid (50 mg every 7 days) until 2 months of age followed by 10 months of PYR (1.25 mg/kg) plus SDX (25 mg/kg every 10 days) and folic acid (50 mg every 7 days)	65.4 patient-years
Capobianco (2014) [59]	Retrospective chart review	Children with congenital toxoplasmosis	Newborns with serologic evidence of <i>T. gondii</i> infection Gestational age median 36 weeks Male 64.5%	31	Infants: PYR, SDZ, folic acid: n = 28 (90.3%) SPY: n = 1 (3.2%) Prednisone: n = 10 (34.5%)	NR
Carellos (2017) [57]	Prospective	Children with congenital toxoplasmosis	Age 56 days Male 55.6%	171	Infants: PYR (1 mg/kg/day for 6 months then thrice weekly) plus SDZ (100 mg/kg/day BID) plus folic acid (7.5 mg thrice weekly)	12

BID twice daily, *CNS* central nervous system, *NR* not reported, *PCR* polymerase chain reaction, *PK* pharmacokinetics, *PYR* pyrimethamine, *SI* SDZ sulfadiazine, *SDX* sulfadoxine, *SMP* sulphamethopyrazine, *SPY* spiramycin, *T. gondii* *Toxoplasma gondii*, *TID* 3 times per day, *TX* treatment

Table 6 Adverse events of pyrimethamine-based therapies for congenital toxoplasmosis

Study (first author, year)	PYR-based treatment	Total AEs	Discontinuation/ change of treatment	Hematologic			Gastrointestinal			Dermatologic	Other
				Neutropenia	Thrombocytopenia	Anemia	Eosinophilia	Nausea and/or vomiting	Diarrhea		
Randomized studies											
McLeod (2006) [47]	TX-A: PS 2 months TX-B: PS 6 months	-	TX-A: 21/57 (37%) TX-B: 20/59 (34%)	-	-	-	-	-	-	-	-
Observational studies											
Faucher (2012) [51]	PYR + SDX	10/121 (8.3%)	5/121 (4.1%)	2/121 (1.7%)	-	1/121 (0.8%)	-	1/121 (0.8%)	-	1/121 (0.8%)	-
Guerina (1994) [48]	PYR + SDZ	15/47 (31.9%)	4/52 (7.7%)	7/47 (14.9%)	-	6/47 (14.9%)	-	-	-	1/47 (2.1%)	-
Hohfeld (1989) [52]	Maternal PYR + SDX Infants PYR + sulfonamides	5/43 (11.6%) 2/54 (3.7%)	-	-	-	Maternal 4/43 (9.3%) Infant 1/54 (1.9%)	-	Maternal 1/43 (2.3%)	-	-	Allergic reaction 1/54 (1.9%)
Lipka (2011) [49]	PS and PYR + SDX	11/24 (45.8%)	12/24 (50%)	11/24 (45.8%)	-	-	-	-	-	-	-
Mombro (1995) [53]	PYR + SMP	3/6 (50%)	3/6 (50%)	-	-	3/6 (50%)	-	-	-	-	-
Schmidt (2006) [67]	PS	7/48 (14.6%)	7/48 (14.6%)	6/48 (12.5%)	-	-	-	-	-	-	Elevated bilirubin 1/48 (2.0%)
Stray-Pedersen (1980) [68]	PS	0/52 (0%)	-	-	-	-	-	-	-	-	-
Hootop (2012) [56]	PS	Maternal 25/119 (21.0%) Infant 0/33 (0%)	-	-	-	-	-	Maternal 25/119 (21%)	-	-	Maternal Hypersensitivity reaction 1/119 (0.8%)
Villena (1998) [55]	PYR + SDX	1/78 (1.3%)	-	-	-	-	-	-	-	1/78 (1.3%)	-

Table 6 continued

Study (first author, year)	PYR-based treatment	Total AEs	Discontinuation/change of treatment	Hematologic			Gastrointestinal			Dermatologic		Other
				Neutropenia	Thrombocytopenia	Anemia	Eosinophilia	Nausea and/or vomiting	Diarrhea	Intolerance	Rash	
Teil [58] (2016)	PYR + SDZ	16/65 (24.6%) (none were attributed to TX)	7/65 (10.8%)	21/65 (32.3%)	5/65 (7.7%)	14/65 (21.5%)	17/65 (26.2%)	7/65 (10.8%)	4/65 (6.2%)	1/65 (1.5%)	1/65 (1.5%)	Agitation 4/65 (6.2%) Erythema 1/65 (1.5%)
Capobiango [59] (2014)	PYR + SDX	37/65 (36.9%) hematologic AEs	-	13/29 (44.8%)	2/29 (6.9%)	2/29 (6.9%)	-	-	-	-	-	Hepatitis 4/29 (13.8%)
Carellos [57] (2017)	PS	16/29 (55.2%)	3/171 (1.8%)	65/171 (37%)	12/171 (7.0%)	28/171 (16.4%)	-	-	-	3/171 (1.8%)	-	Multiple blood disorder 9.4%

Unless otherwise specified, values refer to infant/children

AEs adverse events, PS pyrimethamine plus sulfadiazine, PYR pyrimethamine, SDX sulfadoxine, SDZ sulfadiazine, SMP sulphamethopyrazine, TX treatment

[40], alanine transaminase or aspartate transaminase levels >5 times upper limit of normal (ULN) (9/28; 32.1%) [40], alkaline phosphatase levels >5 times ULN (3/28; 10.7%) [40], hepatotoxicity (2/18; 11.1%) [44], and pancreatic enzyme levels >2 times ULN (6/28; 21.4%) [40]. The outcome of the patient with Steven–Johnson syndrome is not clear as the person was lost to follow-up [45].

3.5 Summary of Adverse Events in Congenital Toxoplasmosis

The search identified 13 studies that reported AEs associated with pyrimethamine-based treatment for congenital toxoplasmosis (Table 5). The studies that reported AEs for pregnant mothers and/or infants/children included a total of 929 infants/children with congenital toxoplasmosis (range 24–171) and a total of 737 pregnant mothers (range 52–685). In the studies that described treatment for infants/children, one was a randomized study [47], ten were prospective [48–57], and two were retrospective [58, 59] in design. The treatment regimens for these studies varied, but all contained pyrimethamine, a sulfonamide, and folic acid, folinic acid, or leucovorin. In the four studies that described maternal treatment [51, 52, 55, 56], mothers were administered spiramycin if infection occurred <16 weeks [56] or <30 weeks [51], or throughout pregnancy if maternal infection was proven or strongly suspected [52, 55]. If seroconversion occurred, indicating maternal infection with *T. gondii*, mothers were given a dosing regimen that contained pyrimethamine plus a sulfonamide and folinic acid until delivery [51, 52, 55, 56]. In general, the length of treatment for infants was 1 year, with the exception of the study of Schmidt et al. [50], which had a duration of treatment of 3 months. Follow-up among all the studies ranged from 6 months to 20 years.

Eight of the 13 studies (61.5%) reported discontinuation or change in treatment due to AEs in infants with congenital toxoplasmosis [47, 49–51, 53, 57, 60, 61] (Table 6). AEs associated with bone marrow suppression in infants/children occurred in ten of the 13 studies (76.9%) [47, 49–53, 57, 59–61] and in mothers occurred in one of two studies [52]. In infant/children, neutropenia was reported in seven studies (53.8%) [47–51, 58, 59], anemia in seven (53.8%) [48, 51–53, 57–59], thrombocytopenia in three (23.1%) [57–59], and eosinophilia in one (7.7%) [58]. Among these studies, the prevalence ranged from 1.7 to 45.8% for neutropenia, from 0.8 to 50.0% for anemia, from 6.9 to 7.7% for thrombocytopenia, and was 26.2% for eosinophilia. One study reported a frequency of anemia of 9.3% in mothers treated with pyrimethamine-based therapy [52].

In infants, GI tract-related AEs were reported in three (23.1%) of the studies, including nausea and/or vomiting

Table 7 Summary of treatment discontinuation/change and adverse events by most common type across manifestations

Manifestation	Discontinued/change in treatment	Bone marrow suppression	Gastrointestinal	Dermatologic
Ocular toxoplasmosis				
Frequency by study	11/11 (100%)	4/11 (36.4%)	4/11 (36.4%)	7/11 (63.6%)
Prevalence, range	2.2–26%	2.8–9.0%	4.2–100%	0.3–11.1%
Toxoplasmic encephalitis				
Frequency by study	4/7 (57.1%)	5/7 (71.4%)	2/7 (28.6%)	4/7 (57.1%)
Prevalence, range	12.1–32.1%	6.6–42.7%	3.4–10.7%	6.3–17.9%
Congenital toxoplasmosis ^a				
Frequency by study	8/13 (61.5%)	10/13 (76.9%)	3/13 (23.1%)	4/13 (30.8%)
Prevalence, range	1.8–50%	0.8–50%	0.8–10.8%	0.8–2.1%

^a Values represent only data from infants

Table 8 Summary of treatment discontinuation/change and adverse events for pyrimethamine plus sulfadiazine and pyrimethamine plus sulfadoxine

Manifestation	Discontinued/change in treatment	Bone marrow suppression	Gastrointestinal	Dermatologic
Pyrimethamine plus sulfadiazine				
Frequency by study	14/19 (73.7%)	11/19 (57.9%)	6/19 (31.6%)	8/19 (42.1%)
Prevalence, range	1.8–50.0%	2.8–45.8%	1.8–100%	1.5–11.0%
Pyrimethamine plus sulfadoxine				
Frequency by study	5/6 (83.3%)	5/6 (83.3%)	3/6 (50.0%)	5/6 (83.3%)
Prevalence, range	2.2–50.0%	0.8–45.8%	0.8–10.8%	0.8–10.8%

Values included for congenital toxoplasmosis were those for infants

($n = 2$), diarrhea ($n = 1$), and GI intolerance ($n = 1$) [51, 57, 58]. The range in the prevalence of nausea and/or vomiting was 0.8–10.8%, and the incidence of diarrhea was 6.2%. GI tract-related AEs reported in mothers treated with pyrimethamine-based therapy were nausea and/or vomiting (21%) and GI intolerance (2.3%) [52, 56].

Across studies, the only dermatologic-related AEs in infants/children were rash, which were reported in four studies (30.8%) (range 0.8–2.1%) [48, 51, 55, 58]. Other AEs reported in infants were allergic reaction/hypersensitivity, elevated bilirubin, agitation, multiple blood disorder, and hepatitis. The prevalence of these AEs was <15% (range 1.9–13.8%). Allergic reaction/hypersensitivity (0.8%) was observed in mothers who were administered pyrimethamine-based treatment in one study [56].

3.6 Summary of Adverse Events Across the Three Manifestations of Toxoplasmosis

The AE profile associated with pyrimethamine-based treatment differed by clinical manifestation of toxoplasmosis. Table 7 summarizes treatment discontinuation/change and the prevalence of the most common types of AEs. Discontinuation and/or change from pyrimethamine-

based treatment was observed in all the included studies for ocular toxoplasmosis (100%) compared with 57.1 and 61.5% for TE and congenital toxoplasmosis, respectively. Up to 50% of patients discontinued or changed therapy because of AEs. Across manifestations, bone marrow suppression and dermatologic AEs were observed in the highest percentage of studies. Bone marrow suppression was lower in studies for ocular toxoplasmosis (36.4%) than for congenital toxoplasmosis (76.9%) and TE (71.4%). A smaller percentage of studies in congenital toxoplasmosis reported dermatologic-related AEs (30.8%) compared with ocular toxoplasmosis (63.6%) and TE (57.1%). In general, across manifestations, GI-associated AEs were less commonly reported than dermatologic and bone marrow suppression-related AEs. Other AEs reported in single studies, irrespective of manifestation, included abnormal levels of liver enzymes, hepatotoxicity, abnormal alkaline phosphate and pancreatic enzyme levels, elevated bilirubin, allergic reaction/hypersensitivity, agitation, abdominal pain, and malaise.

Across the three manifestations of the disease the most commonly used treatment regimens were pyrimethamine plus sulfadiazine ($n = 19$) and pyrimethamine plus sulfadoxine ($n = 6$). All other regimens were evaluated in only

one or two studies. Table 8 summarizes treatment discontinuation or change as well as the prevalence of bone marrow suppression, GI, and dermatologic AEs for pyrimethamine plus sulfadiazine and pyrimethamine plus sulfadoxine. A similar percentage of studies reported discontinuation/change in treatment with pyrimethamine plus sulfadiazine (73.7%) compared with pyrimethamine plus sulfadoxine (83.3%). Pyrimethamine plus sulfadiazine compared with pyrimethamine plus sulfadoxine was associated with a lower percentage of studies reporting bone marrow (57.9 vs 83.3%, respectively), GI (31.6 vs 50.0%), or dermatologic (42.1 vs 83.3%) AEs.

4 Discussion

This systematic review of 2975 patients from 31 studies summarizes the current evidence on the prevalence of AEs associated with pyrimethamine-based treatment regimens used to treat the three main manifestations of toxoplasmosis: ocular toxoplasmosis, congenital toxoplasmosis, and TE. The AE profile associated with pyrimethamine-based treatment across the three manifestations has not previously been systematically reviewed.

The types of AEs observed differed across manifestations. AE-related treatment discontinuation or change in therapy occurred in >55% of the studies, and up to 50% of patients discontinued or changed treatment because of AEs. The most commonly observed AEs among the three manifestations were indicative of inhibition of folate metabolism, that is, bone marrow suppression, dermatologic, and GI. A similar percentage of studies in congenital toxoplasmosis and TE reported bone marrow suppression-related AEs, which was higher than the percentage of studies in ocular toxoplasmosis. The number of studies and patients reporting GI disturbances appeared to be more frequent in ocular toxoplasmosis than either TE or congenital toxoplasmosis. Dermatologic AEs appeared to be less frequent in congenital toxoplasmosis than in ocular toxoplasmosis or TE.

The frequency of specific AEs also varied across manifestations. None of the studies in ocular toxoplasmosis—of which seven of the 11 were randomized trials—reported neutropenia, while 53.8% of the studies in congenital toxoplasmosis reported this AE. Eosinophilia was only observed in studies in congenital toxoplasmosis, and pancytopenia was only seen in TE studies. In contrast, thrombocytopenia was observed in studies across all three manifestations. Of the dermatologic AEs, pyrimethamine-based treatment-associated rash was the most commonly reported. The frequency of Steven–Johnson syndrome was uncommon; Steven–Johnson syndrome was reported in three patients (3/2975 patients; 0.1%) of which two patients

were treated with pyrimethamine plus sulfadoxine for ocular toxoplasmosis and one was treated with pyrimethamine plus sulfadiazine for TE. All three patients were also administered folinic acid. The outcomes of these patients are unknown as they were not reported in the published studies. The most frequently reported GI AEs were diarrhea and nausea/vomiting.

For all manifestations, the most common therapy regimen was pyrimethamine plus sulfadiazine plus folinic acid. Other pyrimethamine-based regimens included sulfadoxine, clindamycin, atovaquone, and TMP-SMX. Compared with pyrimethamine plus sulfadoxine, pyrimethamine plus sulfadiazine was associated with a smaller percentage of studies reporting bone marrow, GI, and dermatologic AEs.

Two studies in TE [44, 45] and five in ocular toxoplasmosis [29, 30, 32–34] assessed the efficacy and safety of non-pyrimethamine-based regimens. These included TMP-SMX and TMP-SMX plus clindamycin, as well as clindamycin and azithromycin monotherapy, clindamycin plus sulfadiazine, and clindamycin plus dexamethasone. For the TMP-SMX-based therapies, reported AEs included neutropenia, diarrhea, minor dermatologic complications, liver impairment, and renal dysfunction in TE ($\leq 22\%$) [44, 45], and rash in ocular toxoplasmosis (2%) [33]. In ocular toxoplasmosis, the clindamycin-based therapies were associated with diarrhea, mild hepatotoxicity, skin rash, and thrombocytopenia (<10%) [29, 32, 34]. The low number of non-pyrimethamine-based regimens in this systematic review precludes the ability to compare the safety profile of the different therapies with each other and with pyrimethamine-based treatments.

Since in all studies pyrimethamine was used in combination with at least one additional drug, it is not possible to know what specific medication was responsible for a given AE. It is probable that a number of the AEs are not due to pyrimethamine. The reasons for the differences in the prevalence of specific AEs among the included studies are not clear, but likely reflect variation in patient populations (i.e., age, immune status, and disease state), drugs coadministered with pyrimethamine, pyrimethamine pharmacokinetics, treatment protocols, and study design. For example, neutropenia was not observed in patients with ocular toxoplasmosis, possibly reflecting the fact this group of patients were immunocompetent adults. The difference in the prevalence of neutropenia between ocular toxoplasmosis and acute TE studies may also, in part, be due to the higher doses of pyrimethamine used for treating TE. The dosages of pyrimethamine used to treat ocular toxoplasmosis (excluding the loading dose) ranged from 25 to 50 mg/day in all 11 included studies. The dosage of pyrimethamine used to treat acute TE was 75 mg/day in four of the seven studies. The safety profile of pyrimethamine may also be affected by age and body weight, which are

known to significantly influence pyrimethamine pharmacokinetics possibly through impacting clearance and the volume of distribution [62, 63]. In addition, pharmacokinetic studies indicate that pyrimethamine serum levels and half-life show wide interpatient variability and differ with age [62, 64, 65], which may also influence the prevalence of AEs. Additional studies are required to gain further insight into the safety profile of pyrimethamine-based treatment of toxoplasmosis.

Our review has limitations. The number of studies and the total sample size analyzed under each manifestation were low. In addition, specific doses, study designs, and patient populations differed among studies within a given manifestation. The great majority of dosing regimens involved pyrimethamine in combination with another drug and this makes it difficult to know how the individual drugs are related to a given AE. The quality of included studies was fair to poor, the randomized controlled trials did not use blinding of treatments, and cohort studies were included, all of which contribute to a higher probability of information bias. However, the inclusion of both prospective observational and retrospective studies, due to the small number of available randomized studies with pyrimethamine, broadens the range of evidence and may improve the generalizability of the findings.

5 Conclusion

This is the first systematic analysis to comprehensively review the safety profile associated with pyrimethamine-based treatments across the three major manifestations of toxoplasmosis. The AE profiles associated with pyrimethamine-based treatments differ by *Toxoplasma* manifestation. In ocular toxoplasmosis and TE, the most frequent AEs were dermatologic, and in congenital toxoplasmosis, the most frequent AEs were associated with bone marrow suppression. Steven–Johnson syndrome was uncommon and reported in only three patients (0.1%). Hematologic AEs occurred in all manifestations and highlight the importance of monitoring the blood of patients administered pyrimethamine-based regimens.

Acknowledgements The authors would like to thank Melissa Giraldo in helping with the literature search.

Compliance with ethical standards

Funding The study was supported by Turing Pharmaceuticals.

Conflict of interest RBH is currently an employee of Turing Pharmaceuticals. EG is a former employee of Turing Pharmaceuticals. EG is currently affiliated with PTC Therapeutics, Inc., South Plainfield, NJ, USA. JC is a former employee of Turing Pharmaceuticals (former SVP, Medical Affairs).

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