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Active Toxoplasmosis Infection: Efficacy and Safety of Treatment Options

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Active Toxoplasmosis Infection: Efficacy and Safety of Treatment Options

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Abstract

This literature review intends to investigate the safety and efficacy of two different drug treatment regimens, pyrimethamine versus trimethoprim-sulfamethoxazole, for active toxoplasmosis infections. Affecting nearly 11% of the United States population and up to 80% of the populations of tropical countries, Toxoplasmosis infection is the second leading cause of death from food borne illness. Current classic management of active infection with pyrimethamine is correlated with numerous undesirable side effects, high cost and need for complex use of adjunctive medications. It is necessary to identify alternative treatment options with fewer side effects, less complex regimens, lower cost, and easier access for patients with active infection. A literature review was performed using electronic search databases including PubMed, CINAHL Complete, Clinical Key, and Embase. Key search terms and MESH terms included toxoplasmosis, toxoplasmosis therapy, toxoplasmosis drugs, toxoplasmosis AND pyrimethamine, toxoplasmosis AND pyrimethamine sulfadiazine, toxoplasmosis AND trimethoprim-sulfamethoxazole. Exclusion criteria consisted of articles not available in English or free of cost, involved use of animals, completed *in vitro,* involved congenital toxoplasmosis, involved pregnant participants or studied latent toxoplasmosis. Following application of inclusion/exclusion criteria a total of six articles were reviewed. Collectively these studies indicate trimethoprim-sulfamethoxazole can be an effective and safe treatment option for active Toxoplasmosis infection in some patient cases; however, it is not clear if trimethoprim-sulfamethoxazole is more effective than the current gold standard treatment of pyrimethamine during the active stage of disease in all patient cases. Overall, further research is recommended.

Keywords: Toxoplasma, *Toxoplasmosis gondii*, pyrimethamine, pyrimethamine/sulfadiazine, trimethoprim/sulfamethoxazole

Introduction

Affecting nearly 11% of the United States population and up to 80% of the populations of tropical countries, Toxoplasmosis infection is the second leading cause of death from food borne illness. Toxoplasmosis infection is caused by the protozoan parasite *Toxoplasma gondii.* This parasite can be found worldwide but is most prevalent in tropical regions of the world with an estimated one third of the human population being infected. The parasite progresses through three infective stages throughout it's lifespan including: active tachyzoite, latent bradyzoite cysts, and sporozoite oocysts. Sporozoite oocysts are most commonly shed in the fecal matter of cats. This parasitic infection has multiple transmission routes including fecal-oral routes, consumption of infected livestock meat, contact with infected soil or water, blood transfusions, organ transplants, and vertical gestational. Infection with this parasite can result in numerous disease types including but not limited to ocular toxoplasmosis, toxoplasmosis encephalopathy, toxoplasmosis lymphadenopathy and congenital toxoplasmosis. Symptomatic presentation occurs most commonly in immunocompromised individuals (CDC, 2018; Dynamed, 2022).

Statement of the Problem

Active Toxoplasmosis infection has been managed with the classic treatment of pyrimethamine for many years however this treatment causes numerous undesired side effects, including but not limited to severe skin rash, bone marrow suppression, and hepatocellular injury

which requires use adjunctive medications and can have extended treatment durations with high costs. Further, the pyrimethamine combo therapy is often not accessible in many remote regions of the world. Further research is needed to identify alternative treatment options for active toxoplasmosis infections with fewer side effects, less complex regimens, lower cost, and easier access.

Research Question

In patients with toxoplasmosis infection is trimethoprim-sulfamethoxazole more effective &/or than the current gold standard treatment of pyrimethamine during the active stage of disease?

Research Methods

A literature review was completed using multiple online resources made available by the University of North Dakota School of Medicine and Health Sciences library. The PubMed, CINAHL Complete, Clinical Key, and Embase databases were searched with filters set between the years of 2010-2022. Key words and MESH terms used included: toxoplasmosis, toxoplasmosis therapy, toxoplasmosis drugs, toxoplasmosis AND pyrimethamine, toxoplasmosis AND pyrimethamine sulfadiazine, toxoplasmosis AND trimethoprim-sulfamethoxazole. Filters used included full text, free, peer reviewed, randomized controlled trial, prospective, and retrospective. PubMed produced 19 results with the above filters. CINHL Complete produced three results with the above filters. Clinical Key produced 29 results with the above filters. Between one and three duplicate articles were identified when comparing search results between each database. Additional articles were identified through review of reference lists of database

resulted randomized controlled trials, meta-analyses, and systematic reviews of the above search terms. Other additional articles were selected using the "similar articles" feature available through PubMed. Excluded articles were not available in English, not available free of cost, involved use of animals, completed *in vitro,* involved congenital toxoplasmosis, involved pregnant participants or studied latent toxoplasmosis. Following exclusions a total of six articles remained for inclusion in this review.

Literature Review

Efficacy of trimethoprim/sulfamethoxazole

Soheilian et al., (2005) desired to identify alternative treatment regimens for ocular toxoplasmosis due to factors such as prevention of irreversible ocular damage, limited access to classical treatment of pyrimethamine/sulfamethoxazole, the high cost associated with the classic treatment, the complexity and high toxicity associated with the classic treatment. The study compared the efficacy of trimethoprim/sulfamethoxazole (TMP/SMX) treatment with the classic pyrimethamine/sulfadiazine treatment therapy. This prospective, randomized, controlled, single-blind clinical trial initially enrolled 71 patients with active ocular toxoplasmosis infections from a specialized uveitis medical center in Tehran, Iran. Of these, 12 patients were excluded from final analysis due to incomplete follow-up (10) or discovery of drug allergies (2). The population studied included the remaining 59 patients. There were 36 male and 23 female participants ranging in age from 12 years old to 59 years old. Included participants were required to have retinal lesions of specific sizes and located in specific, defined zones of the eye. Participants could not have a documented allergy to the treatments being used and could not be diagnosed

with any subsequent ocular diseases. Additional exclusion criteria were fellow eye visual acuity of <20/200, central macular lesion location, leukopenia <5000, and thrombocytopenia <120,000/ml.

Computer randomization software was used to divide participants into two groups of equal male to female ratios. The classic treatment of pyrimethamine/sulfadiazine, considered the control group, had 29 patients with a mean age of 23.5 +/- 7.4 years. The TMP/SMX treatment group had 30 patients with a mean age of 26.6 +/- 11.7 years. Treatment duration was six weeks for both groups with data collected at day one and at the end of each week. All drugs were distributed in similar packaging with either a "1" label indicating the control group or a "2" indicating the TMP/SMX group. Participants and masked researchers remained unaware of which group each label identified. All physical examinations were completed by an unmasked ophthalmologist. Study outcome measures were collected by masked retina specialists. The primary outcome measure of retinochoroidal lesion size was measured using fundus photography completed on day one and after six weeks of treatment. Secondary outcome measures of vitreous inflammation and visual acuity were measured using slit lamp and indirect ophthalmoscopy procedures and protocols designed and published in the literature. Enzyme-linked immunosorbent assay (ELISA) was used for the secondary outcome measure of serum antitoxoplasmosis antibodies IgM and IgG. All participants in the classic treatment group underwent weekly lab work including complete blood cell and platelet counts as is required for routine drug monitoring during use of pyrimethamine/sulfadiazine. Monitoring for adverse drug reactions occurred continuously throughout the study and follow-up time frame. Following the

completion of the six week treatment regimen participants were monitored every three months over the course of two years to identify recurrence rate.

Statistical analysis of the data included use of the independent-sample *t* test, the chi-square test, the paired *t* test and the McNemar test. Clinical significance was defined with p values <0.05. Adequate fundus photographs were not obtained from ten participants, five from each treatment group, and were thus not included in the primary outcome measures for retinochoroidal lesion size. Following six weeks of treatment, no significant difference was identified between the study groups in regards to retinal lesion size reduction. The mean size reduction of the lesion was 61% in the classic group and 59% in the TMP/SMX group (p=0.75). Following six weeks of treatment, vitreous inflammation was reduced to levels of trace to no inflammation in 69% (n=20) of the classic therapy group and 56.7% (n=17) of the TMP/SMX group. There was no significance identified between the two groups (p=0.24). Significant improvements in visual acuity occurred within each group. Classic therapy improved 0.56 logMAR units (p<0.01). TMP/SMX therapy improved 0.52 logMAR units (p<0.01). There was no significance in visual acuity improvement between groups (p=0.75). ELISA testing identified all participants as positive for IgG. IgM was identified in 44.8% (n=13) of the control group and 30% (n=9) of the TMP/SMX group (p=0.18). Overall, results of this study support the use of TMP/SMX in place of classic pyrimethamine/sulfadiazine for the treatment of ocular toxoplasmosis with lesions within the zones studied (Soheilian et al., 2005).

Strengths of the study include: The prospective, randomized, controlled, single-blind nature of this study add to it's overall strength. The treatment duration of this study was carried

out for a longer period of time than previous studies adding necessary data regarding treatment of ocular toxoplasmosis infection. There is no apparent bias or propriety identified.

Weakness of the study include: It is unclear whether all participants were of Iranian decent. This limits the ability to generalize this data with wider populations. This study was unable to fully mask all of the evaluating physicians. The additional weekly testing of complete blood cell and platelet counts in the control group could be viewed as weakening of the blinded nature of this study. The authors were unable to collect fundus photographs from all of the participants which weakens the strength of the primary outcome measure. The assumption was made that the classic therapy group "is effective in promoting resolution of toxoplasmic retinochoroiditis" with neither of the treatments being compared to an untreated, natural course of infection. Finally, larger sample sizes are necessary for further evaluation of adverse effects of both drugs.

Alavi et al., (2010) desired to identify effective treatment of toxoplasmic lymphadenitis. The study aimed to determine whether TMP/SMX has the same therapeutic effectiveness in treating this presentation of toxoplasmosis infection as seen in treatment of the cerebral and ocular forms of the disease. This randomized, double-blind, placebo-controlled study was completed between 2005-2007 at the Infectious Disease Clinic of Ahvaz, Iran. Inclusion criteria was based on clinical presentation of lymphadenitis which was confirmed to be of toxoplasmosis origin via serologic and histopathological studies. Exclusion criteria were: known drug allergies to the experimental medication, current comorbid infection, pregnancy, actively breastfeeding, or treatment with an antibiotic within the past month.

Fifty one eligible participants were identified to meet the inclusion criteria however five people declined to participate prior to beginning. The forty six remaining participants were randomly divided into two equally sized study groups. The experimental group (n=23; 65.2% male, n=15; 34.8% female, n=8) received TMP/SMX dosed per bodyweight twice per day for four weeks. The age distribution of the experimental group included 65.2% (n=15) ages less than 15 years old, 26.1% (n=6) ages between 15-25 years old, and 8.7% (n=2) ages greater than 25 years old. The placebo-control group (n=23; 73.9% male, n=17; 26.1% female, n=6) received an identical appearing, inactive tablet twice per day for four weeks. The age distribution of the placebo-control group included 73.9% (n=17) ages less than 15 years old, 17.4% (n=4) ages between 15-25 years old, and 8.7% (n=2) ages greater than 25 years old. Follow-up monitoring and data collection was completed by all participants and occurred at the conclusion of one, three, and six months.

The primary outcome measure was response to treatment which was defined as satisfactory, with non-palpable lymphadenopathy and IgM <6 IU, or unsatisfactory, with no clinical or laboratory improvement. After four weeks of treatment the experimental group showed a 65.2% (n=15) clinical and serological response rate while the control groups showed a 13.1% (n=3) clinical and serological response rate. These results identified a significant difference in treatment effectiveness between the study groups (52.2%; $p<0.001$). At the final six month follow-up the experimental group showed a 87.0% (n=20) clinical and serological response rate while the control groups showed a 43.5%% (n=10) clinical and serological response rate; a difference of 46.4%; $p=0.002$. Overall, the results of this study support the use of

TMP/SMX in the treatment of toxoplasmic lymphadenitis with the goal of shortening infection duration and preventing extended antibiotic use (Alavi et al., 2010).

Strengths of the study include: The randomized, double-blind, placebo-controlled nature of the study added to its overall strength. All participants who began the study were able to complete it. The study was funded by the Infectious and Tropical Disease Research Center at the Kerman University of Medical Sciences in Kerman, Iran. No conflict of interest was disclosed.

Weakness of the study include: It is unclear whether all participants were of Iranian decent. This limits the ability to generalize this data with wider populations as all participants were recruited from a single infectious disease clinic in southwest Iran. The sample size of the study was small and there was a lack of direct comparison of TMP/SMX to the current first line treatment of pyrimethamine/sulfadiazine.

Francis et al., (2004) completed a prospective study intended to support previously published data regarding the efficacy of TMP/SMX in the treatment of toxoplasma encephalitis in AIDs patients. Twenty HIV-positive patients (50%, n=10 males; 50%, n=10 females; mean age 32 years old) were referred for study participation following identification of toxoplasmosis-like lesions on computed tomography (CT) scans. HIV status was confirmed via HIV enzyme-linked immunosorbent assay (ELISA); CD4 counts were only obtained from seven participants. Toxoplasma gondii antibodies were only positive in eight participants. The ethnicity of the participants was not discussed however researchers make note of a southeastern province of South Africa as needing alternative treatment options for toxoplasma encephalitis due to little to no access to IV administration of the classic treatment as one purpose of the study.

All participants received the same intervention of TMP-SMX administered four times daily for four months followed by a twice daily long-term dose if the participant was not already completing daily antiretroviral therapy due to HIV status. Data was not presented on which participants continued with TMP-SMX versus antiretroviral therapy. Follow-up CT scans were completed between two to four weeks after beginning treatment to identify radiologic changes. It is unclear what determined when in the two to four week timeframe each participant completed rescanning. If patients displayed clinical improvement, it was assumed the diagnosis of Toxoplasma encephalitis was correct. Participants with absence of clinical or radiologic improvement were referred to neurology for further evaluation/treatment and were discontinued in study follow-up. It is unclear how many participants initially began the study or how many were lost to follow up for the various reasons listed as the researchers only discuss how 20 participants completed the study. Statistical analysis is mentioned as being completed however no actual data is presented in this article. This omission decreases the strength of the presented study outcomes. The study claims to "establish the efficacy of oral co-trimoxazole as therapy for acute cerebral toxoplasmosis" (Francis et al., 2004).

Strengths of the study include: Limited supporting data by way of CT imaging showing improvement in suspected Toxoplasma encephalitis lesions when treated with TMP-SMX. Presentation of actual data within the article may contribute to further strength of outcomes claimed.

Weakness of the study include: In addition to the low N value of this study the main weakness is the lack of clinical and statistical comparison to a control or alternative treatment group. There is difficulty generalizing the results to the greater population due to unclear

demographics studied. There is also speculation as to if all the included participants truly had an active Toxoplasma infection and an unclear number of participants were lost to follow-up. Unfortunately, this study leaves the reader with far more questions than answers.

Kongsaengdao et al., (2008) completed a randomized controlled trial with the goal of identifying a most effective treatment regimen for toxoplasmic encephalitis in AIDS patients. Determining a specific, optimal dosing of pyrimethamine with sulfadiazine versus safety and efficacy of TMP-SMX would fill a gap in the literature of the time. Thirty-two HIV/AIDS patients were initially enrolled in the prospective study. Only participants with a CD4 count less than 200 cell/mm3 and clinical toxoplasmic encephalitis were included. Two were excluded due to CT findings which met exclusion criteria. Participants were randomly assigned to one of three study groups. The P50-S group (n=10; mean age 39.6 years old with a standard deviation of 9.4 years; 70% male, n=7; 30% female, n=3) received pyrimethamine 50mg/sulfadiazine 4g per day. The P100-S group (n=10; mean age 38.2 years old with a standard deviation of 9.3 years; 80% male, n=8; 20% female, n=2) received pyrimethamine 100mg/sulfadiazine 4g per day. The TMP-SMX group (n=10; mean age 34.2 years old with a standard deviation of 10.7 years; 40% male, n=4; 60% female, n=6) received trimethoprim 10mg/kg/day with sulfamethoxazole 50mg/kg/day. There was no blinding of the experimental groups and no control group in the study. Treatment and monitoring duration in all groups was six weeks. Serum titer for *Toxoplasma gondii* and CD4 counts were measured via standard lab processing for all participants prior to initiating the study. Routine monitoring of CBC and platelet count to identify any bone marrow suppression which is a commonly found side effect of pyrimethamine/sulfadiazine treatment was completed for all participants throughout the study. Further definition of “routine” was not

described, nor was this precise data presented in the paper. The primary outcome measure determining treatment effectiveness was measured by occurrence of death during the six week study period. Effort was made to determine whether cause of death was directly related to the active toxoplasma encephalitis infection or if other factors were predominant. Successful treatment was measured by repeat a CT scan completed two weeks after initialing treatment followed by completion of a lumbar puncture to evaluate *Toxoplasma gondii* IgG antibodies.

Statistical analysis of data collected was completed with the STATA v6.0 program. There was no statistical difference found when comparing demographics of each group (Age p=0.44; Gender p=0.16; CD4 count p=0.54; HIV viral load p=0.3). The primary outcome measure of death during treatment with TMP-SMX was 30% (n=3, p=0.05) indicating a 70% treatment success rate. Pertinent results data for the other study groups and outcome measures are presented under aligning topic sections below. Overall, this study found no significant difference in efficacy between the three treatment regimens. This lends support to the use of TMP-SMX for effective treatment of Toxoplasmic encephalitis infection affecting HIV positive patients in regions in which pyrimethamine/sulfadiazine is not available or reasonable for use based upon its side effect profile. The authors do make note of the need for further studies evaluating the use of IV versus oral TMP-SMX in the treatment of Toxoplasmic encephalitis infections (Kongsaengdao et al., 2008).

Strengths of the study include: There was no statistically significant variation between the three study groups. There were no conflicts of interest declared.

Weakness of the study include: There was no blinding of the study groups and some patients were receiving highly active antiretroviral therapy (HAART) for their HIV while others

were not. Details regarding the HAART treatments or how many participants received them was not described as it's potential effects on study outcomes taken into consideration. The overall duration of the study was short at only six weeks. Premature study termination is mentioned at numerous points however no further details explaining why are offered.

Efficacy of pyrimethamine

Ghavidel et al., (2017) compared pyrimethamine/sulfadiazine versus azithromycin treatment in participants with ocular toxoplasmosis in the north west region of Iran. Through their review of literature, they identified ocular toxoplasmosis having a prevalence of 33% world wide and 54.5% within their home nation of Iran. Classic treatment of toxoplasmosis infection is identified as pyrimethamine plus a combination of two to three additional medications serving as both supportive and side effect therapy. This results in a challenging and expensive treatment regimen which many patients in Northern Iran are unable to access, afford or tolerate.

The researchers sought to investigate alternative treatment options for ocular toxoplasmosis due to this high prevalence of drug intolerance, adverse drug reactions and overall inaccessibility to the classic treatment. A prospective, single-blind, randomized control clinical trial was completed between January 2014 and October 2016 at the Nikookari hospital in Tabriz, Iran. Seventy two participants with active, non-vision threatening toxoplasimic chorioretinitis met the inclusion criteria and agreed to participate. Ages ranged from 20-60 years old. Participants were divided into two equal groups using a computer generated randomizer. One group (n=36; mean age 37.56 years old; 55.4% male, n=20; 44.6% female, n=16) received classic treatment of pyrimethamine/ sulfadiazine. The other group (n=36; mean age 41.94 years old; 50% male, n=18; 50% female,

n=18) received azithromycin. The was no control placebo group. Treatment duration was six weeks with a 24 month follow up. The main outcome measured in the study was retinochoroidal lesion size change which was every two weeks via fundus photography by an ophthalmologist. Additional outcome measures included: time to disease inactivity which was defined as lesion borders sharpening and scarring; disease reoccurrence rate which was defined as occurrence of new "active necrotizing chorioretinal lesion(s) adjacent to an old scar or elsewhere"; changes in visual acuity; and adverse drug reactions. For the purposes of this literature review, only data related solely to the pyrimethamine/sulfadiazine group was presented. Within the pyrimethamine/sulfadiazine group, retinal lesion sizes reduced collectively by 638.89 micrometers (65.7%) indicating significant efficacy of this treatment regimen. A visual acuity improvement of 0.39 logMAR units (20/49 Snellen acuity; p=0.00) was found with an infection reoccurrence rate of 11.1% (n=4) within the 24 month follow up time. This study adds supporting data to the efficacy of the classic treatment regimen of pyrimethamine/sulfadiazine in the treatment of ocular toxoplasmosis (Ghavidel et al., 2017).

Strengths of the study include: This randomized, controlled study included groups which shared comparable demographics and all participants completed the study in its entirety. This study was completed ethically and the authors declared no conflicts of interest.

Weaknesses of the study include: Overall, this study used a small sample size which was only single-blind. There was no placebo control group with a short follow-up monitoring duration. Lastly, there is a reduced ability to generalize to the world-wide population due to demographics studied in a single North Iran hospital.

In a study by Soheilian et al., (2005), described in full above, the efficacy of TMP/SMX treatment was compared to treatment with pyrimethamine/sulfadiazine in active cases of ocular toxoplasmosis infection. As stated above, following six weeks of treatment, no significant difference was identified between the study groups in regards to retinal lesion size reduction. Mean 61% lesion size reduction in the classic group and mean 59% lesion size reduction in the TMP/SMX group ($p=0.75$). Following 6 weeks of treatment, vitreous inflammation was reduced to levels of trace to no inflammation in 69% (n=20) of the classic therapy group and 56.7% (n=17) of the TMP/SMX group. There was no significance identified between the two groups ($p=0.24$). Significant improvements in visual acuity occurred within each group. Classic therapy improved 0.56 logMAR units ($p<0.01$). TMP/SMX therapy improved 0.52 logMAR units ($p<0.01$). There was no significance in visual acuity improvement between groups ($p=0.75$). ELISA testing identified all participants as positive for IgG. IgM was identified in 44.8% (n=13) of the control group and 30% (n=9) of the TMP/SMX group ($p=0.18$). Overall, results of this study found pyrimethamine/sulfadiazine treatment to have similar effectiveness as the experimental drug for the treatment of ocular toxoplasmosis with lesions within the zones studied (Soheilian et al., 2005).

In a study by Kongsaengdao et al., (2008), described in full above, two different doses of pyrimethamine/sulfadiazine were compared with TMP-SMX. As stated above, the P50-S group (n=10; mean age 39.6 years old with a standard deviation of 9.4 years; 70% male, n=7; 30% female, n=3) received pyrimethamine 50mg/sulfadiazine 4g per day. The P100-S group (n=10; mean age 38.2 years old with a standard deviation of 9.3 years; 80% male, n=8; 20% female, n=2) received pyrimethamine 100mg/sulfadiazine 4g per day. Routine monitoring of CBC and

platelet count to identify any bone marrow suppression which is a commonly found side effect of pyrimethamine/sulfadiazine treatment was completed for all participants throughout the study. Further definition of "routine" was not described, nor was this precise data presented in the paper. The primary outcome measure of death during treatment with P50-S group was 0% (n=0, p=0.05) The primary outcome measure of death during treatment with P100-S was 10% (n=1, p=0.05). Overall, this study found no significant difference in efficacy between the three treatment regimens. Despite lack of significance, as the P50-S group resulted in 0% death rate, this dose is suggested to have more optimal outcomes than the P100-S dose (Kongsaengdao et al., 2008).

Safety of trimethoprim/sulfamethoxazole

Shammaa et al., (2021) studied adverse events related to a wide variety of medications reported in the treatment of Toxoplasma gondii infections. This retrospective study analyzed data from the FDA adverse event reporting system (FAERS) between 2013-2019. All data was collected from the FDA website. Within the timeframe noted there were 503 reported cases of Toxoplasma gondii infection which had "one or more of seven types of outcomes" as classified within the FAERS. For the purposes of the study, all available data was recategorized into two outcome groups: Death (DE) and Serious (SE). Ages of patients reported span from newborn to ">60". The adult age group, those 20-60 years old, was 60% (n=301) of the data. The over 60 years age group was 18% (n=89) of the study. The study consisted of 46% (n=245) females, 49% (n=233) males and 5% (n=25) unknown sex. The FAERS database included reports of adverse drug events (ADEs) in the treatment of Toxoplasma infections from around the world with 38%

(n=193) coming from the United States, 28% (n=142) coming from France, 31% (n=154) coming from “other countries” and 3% (n=14) coming from “unknown” countries. Reports to the FAERS are accepted from physicians, pharmacists, “other health professionals” and consumers.

The study found 897 different drugs reported for use in the treatment of unspecified Toxoplasma infections. For the purposes of this literature review, only data relating to TMP/SMX and pyrimethamine based therapy will be presented. Statistical analysis was presented via reporting odds ratio (ROR) for death with a confidence interval (CI) of 95% for each of the drugs selected. Though not significant, ROR for death in patients treated with TMP/SMX was 1.59; 0.81-3.16: p=0.1796 making it the third most likely Toxoplasmosis treatment in this study to have a death outcome. ROR with a 95% CI was also calculated for the most commonly reported ADEs. ADEs with RORs less than one associated with the use of TMP/SMX, indicating lower risk of experiencing the symptom, included: vomiting, rash, pyrexia, pancytopenia, neutropenia, and nausea. ADE of hepatocellular injury was the only ROR for TMP/SMX found to be greater than one, indicating greater risk of experiencing the event during treatment. Further study is needed to better understand the risks versus benefits of treatment with TMP/SMX given the often multifactorial nature of patients with Toxoplasmosis infection (Shammaa et al., 2021).

Strengths of the study include: This study filled a gap in available literature comparing and analyzing multiple treatment options for Toxoplasma infections. Support of previously published results on some drugs included was found. Overall, this study had a sufficiently high N value. There were no reported funding sources or conflicts of interest declared.

Weaknesses of the study include: The FAERS is a spontaneous reporting system making it possible for an incomplete or biased presentation of the data dependent on the willingness of

people volunteering to submit the ADE report. Precise maximum age of patients over the age of 60 years is not specified. The age unknown group was 17% (n=86). Data indicating the specific type of Toxoplasmosis infection and specific dosages of the reported drugs was not available; neither was therapies for comorbid conditions each patient may have been experiencing.

In a study by Soheilian et al., (2005), described in full above, the efficacy of TMP/SMX treatment was compared to treatment with pyrimethamine/sulfadiazine in active cases of ocular toxoplasmosis infection. An additional outcome measure was adverse drug reactions during the treatment period and the two year follow up monitoring period of the study. Of the 30 participants in the TMP/SMX treatment group, 2.8% (n=1) experienced an adverse reaction described as a rash. This treatment was discontinued for this participant and they were excluded from further follow up in the study. When compared to the pyrimethamine/sulfadiazine group there was no significance in this adverse occurrence (p=0.98) (Soheilian et. al., 2005).

In a study by Kongsaengdao et al., (2008), described in full above, TMP-SMX was compared with two different doses of pyrimethamine/sulfadiazine. As stated previously, an additional outcome measure was adverse drug reactions during the six week treatment period. Results presented for the secondary outcome measure of drug allergy during treatment with TMP-SMX was 0% (n=0, p=0.05**)** Bone marrow suppression in the TMP-SMX group was 0% (n=0) (Kongsaengdao et al., 2008). These findings support the safety of TMP-SMX use for this treatment duration.

Safety of pyrimethamine

In a study by Soheilian et al., (2005), described in full above, the efficacy of TMP/SMX treatment was compared to treatment with pyrimethamine/sulfadiazine in active cases of ocular toxoplasmosis infection. As stated previously, an additional outcome measure was adverse drug reactions during the treatment period and the two year follow up monitoring period of the study. Of the 29 participants in the pyrimethamine/sulfadiazine treatment group, 2.9% (n=1) experienced an adverse reaction described as a rash. This treatment was discontinued for this participant and they were excluded from further follow up in the study. When compared to the TMP/SMX group there was no significance in this adverse occurrence (p=0.98) (Soheilian et al., 2005).

In a study by Kongsaengdao et al., (2008), described in full above, two different doses of pyrimethamine/sulfadiazine were compared with TMP-SMX. As stated previously, an additional outcome measure was adverse drug reactions during the treatment period. Results presented for the secondary outcome measure of drug allergy with severe skin rash during treatment in the P50-S group was 30% (n=3**).** Bone marrow suppression in the P50-S group was 0% (n=0). The secondary outcome measure of drug allergy with severe skin rash in the P100-S group was 20% (n=2**).** Bone marrow suppression in the P100-S group was 20% (n=2) (Kongsaengdao et al., 2008). These findings add important data when considering safety of pyrimethamine/sulfadiazine use for this treatment duration.

In a study by Ghavidel et al., (2017), described in full above, pyrimethamine/sulfadiazine was compared to an alternative treatment in participants with ocular toxoplasmosis. An additional outcome measure of this study was adverse drug reactions among the participants

during the study. In the pyrimethamine/sulfadiazine group, adverse drug reactions occurred in 55.5% (n=20). The adverse reactions were further divided by type and described as n=16 with gastrointestinal symptoms and n=4 with dizziness. These findings were highly significant (p=0.00) (Ghavidel et al., 2017).

In a study by Shammaa et al., (2021), described in full above, ADRs related to a wide variety of medications reported in the treatment of *Toxoplasma gondii* infections were retrospectively studied. Statistical analysis was presented via reporting odds ratio (ROR) for death with a confidence interval (CI) of 95% for each of the drugs selected. Though not significant, ROR for death in patients treated with pyrimethamine was 1.53; 0.99-2.36: p=0.056 making it the second most likely Toxoplasmosis treatment in this study to have a death outcome. ROR for death in patients treated with pyrimethamine-sulfadiazine was 0.19; 0.06-0.62: p-value not available; this indicates a decreased risk of death when Toxoplasmosis infection is treated with this combination. ROR with a 95% CI was also calculated for the most commonly reported ADEs. ADEs with RORs less than one associated with the use of pyrimethamine, indicating lower risk of experiencing the symptom, included: rash, pancytopenia, neutropenia, hepatocellular injury, and eosinophilia with systemic symptoms. ADEs of vomiting, pyrexia, and nausea were the RORs for pyrimethamine found to be greater than one, indicating greater risk of experiencing the event during treatment. ADEs with RORs less than one associated with the use of pyrimethamine-sulfadiazine, indicating lower risk of experiencing the symptom, included: vomiting, pyrexia, and nausea. ADEs of rash, pancytopenia, neutropenia, hepatocellular injury and eosinophilia with systemic symptoms were the RORs for pyrimethamine-sulfadiazine found to be greater than one, indicating greater risk of experiencing the event during treatment. Though

results of this study support previous findings of pyrimethamine treatment for Toxoplasma infection to be associated with the most ADEs it was not found to be associated with the highest risk of death. Further study is needed to better understand the risks versus benefits of treatment with pyrimethamine given the often multifactorial nature of patients with Toxoplasmosis infection (Shammaa et al., 2021).

Discussion

Efficacy of TMP/SMX

Four studies, published between 2005 and 2010 were analyzed for the efficacy of TMP/SMX use in the treatment of active Toxoplasmosis infection. All four studies identified efficacy of TMP/SMX in successful treatment of the studied presentation of active toxoplasma infection (Francis et al., 2004; Soheilian et al., 2005; Kongsaengdao et al., 2008; Alavi et al., 2010). It should be noted two studies looked at treatment of the encephalitis presentation of the infection; one for a four month treatment duration (Francis et al., 2004) and one for a six week treatment duration (Kongsaengdao et al., 2008). One study looked at a six week treatment of the ocular presentation of the infection (Soheilian et al., 2005). One study looked at a four week treatment of the lymphadenitis presentation of the infection (Alavi et al., 2010). Two studies compared TMP/SMX treatment with pyrimethamine/sulfadiazine treatment and found no significant difference between effectiveness (Soheilian et al., 2005; Kongsaengdao et al., 2008). The study by Alavi et al., (2010) was compared to a placebo control treatment group. The study by Francis et al., (2008) only assessed TMP/SMX treatment with no comparison to placebo or alternative

treatments. Collectively, the data presented in these studies support the use of TMP/SMX for effective treatment of a variety of presentations of active Toxoplasma infection.

Efficacy of pyrimethamine/sulfadiazine

Three studies, published between 2005 and 2017 were analyzed for the efficacy of pyrimethamine/sulfadiazine use in the treatment of active Toxoplasmosis infection. All three studies identified efficacy of pyrimethamine/sulfadiazine in successful treatment of the studied presentation of active toxoplasma infection (Soheilian et al., 2005; Kongsaengdao et al., 2008; Ghavidel et al., 2017). It should be noted two studies looked at treatment of the ocular presentation of the infection; both for a six week treatment duration (Soheilian et al., 2005; Ghavidel et al., 2017). One study looked at treatment of the encephalitis presentation of the infection for a six week treatment duration (Kongsaengdao et al., 2008). Two studies compared pyrimethamine/sulfadiazine treatment with TMP/SMX treatment and found no significant difference between effectiveness (Soheilian et al., 2005; Kongsaengdao et al., 2008). The study by Ghavidel et al., (2017) was compared to Azithromycin treatment without a placebo control treatment group. Collectively, the data presented in these studies support the continued use of pyrimethamine/sulfadiazine for effective treatment of a variety of presentations of active Toxoplasma infection.

Safety of TMP/SMX

Three studies, published between 2005 and 2021 were analyzed for the safety of TMP/SMX use in the treatment of active Toxoplasmosis infection. Two studies identified occurrence of adverse side effects with use of TMP/SMX for treatment of the studied presentation of active

toxoplasma infection (Soheilian et al., 2005; Shammaa et al., 2021). The Soheilian et al., (2005) study looked at a six week treatment of the ocular presentation of Toxoplasmosis infection and found only one TMP/SMX treatment group participant who experienced a rash of unspecified severity. The Shammaa et al., (2021) study included undetermined treatment durations of a variety of active Toxoplasmosis infection presentations and found the greatest risk of hepatocellular injury in patients treated with TMP/SMX. Symptoms such as vomiting, rash, pyrexia, pancytopenia, neutropenia, and nausea occurred in other patients but were significantly less likely compared to other treatment regimens analyzed (Shammaa et al., 2021). Interestingly, the Shammaa et al., (2021) study also found the TMP/SMX treatment to be the third highest likelihood of resulting in patient death if used to treat active Toxoplasmosis infection of unspecified presentation type. The study by Kongaengdao et al., (2008), which looked at the encephalitis presentation of active Toxoplasmosis infection, found no severe skin rash or bone marrow suppression reactions in any participants treated with TMP/SMX. It is unclear if the study by Kongaengdao et al., (2008) did not have occurrences of adverse side effects or chose not to document side effects other than severe skin reaction or bone marrow suppression. Overall, it is important to be cognizant of the multitude of various side effects TMP/SMX may have and to weigh the risks/benefits of use in treatment of a patient.

Safety of pyrimethamine/sulfadiazine

Four studies, published between 2005 and 2021 were analyzed for the safety of pyrimethamine/sulfadiazine use in the treatment of active Toxoplasmosis infection. All four studies identified adverse side effects with the use of pyrimethamine/sulfadiazine in treatment of

the studied presentations of active toxoplasma infection (Soheilian et al., 2005; Kongsaengdao et al., 2008; Ghavidel et al., 2017; Shammaa et al., 2021). Soheilian et al., (2005) found an insignificant 2.9% of pyrimethamine/sulfadiazine treatment group participants experienced a rash of unspecified severity. Ghavidel et al. (2017) found a significant 55.5% of study participants experiencing an adverse side effect; of the 20 participants with adverse side effects, 16 reported gastrointestinal upset and 4 reported dizziness. Kongsaengdao et al., (2008) compared two different pyrimethamine/sulfadiazine treatment dosages and found both groups experienced adverse, severe skin rashes. Bone marrow suppression was only identified in the higher dosage group (Kongaengado et al., 2008). Shammaa et al., (2021) presented data on undetermined treatment durations of a variety of active Toxoplasmosis infection presentations. Infections treated with pyrimethamine only were identified of having a significantly lower risk of rash, pancytopenia, neutropenia, hepatocellular injury, and eosinophilia with systemic symptoms; however, there was a significantly greater risk of vomiting, pyrexia, and nausea. Infections treated with pyrimethamine/sulfadiazine were identified as having a significantly lower risk vomiting, pyrexia, and nausea; however, a significantly greater risk of rash, pancytopenia, neutropenia, hepatocellular injury and eosinophilia with systemic symptoms (Shammaa et al., 2021). This study also found the pyrimethamine mono-treatment to be the second highest likelihood of resulting in patient death if used to treat active Toxoplasmosis infection of unspecified presentation type while the pyrimethamine/sulfadiazine combination treatment had a decreased likelihood of a death outcome (Shammaa et al., 2021). As stated previously and with all drug therapies, it is important to be cognizant of the multitude of various side effects

pyrimethamine/sulfadiazine may have and to weigh the risks/benefits of use in treatment of a patient.

Reliability of studies

This literature review identified six studies of varying degrees of strength. Though efforts were taken to identify the strongest studies if a study met the inclusion criteria presented above it was not excluded due to lower reliability. Only one study was identified as being poor despite meeting the inclusion criteria. The prospective, randomized, controlled study by Soheilian et al., (2005) utilized a treatment duration of six weeks which was a longer period of time than previous studies at the time and is comparable to the other studies included in this review. The strength of the single-blinding in this study is debatable due to the additional weekly monitoring the control group underwent.

The randomized, controlled study by Ghavidel et al., (2017) and the randomized, double-blind, placebo-controlled study by Alavi et al., (2010) both had a smaller N values however no participants were lost throughout the duration of the study and the demographics of each study group were comparable.

The randomized, controlled study by Kongaengdao et al., (2008) utilized three study groups with no statistically significant variation between them. Treatment duration was six weeks, similar to other studies, and the comparison of two different pyrimethamine dosages to TMP/SMX is a valuable contribution to the literature. Unfortunately, this study lacked blinding and some patients were receiving highly active antiretroviral therapy (HAART) for HIV which makes the results less generalizable to a broader population.

Shammaa et al., (2021) compared and analyzed multiple treatment options for Toxoplasma infections and included safety and effectiveness for a variety infection presentations. This study is the most current and included the greatest N value making it the strongest article presented here for the topic of treatment safety. Support of previously published results on some drugs included was found. Despite this, it should be noted the FAERS is a spontaneous reporting system making it possible for an incomplete or biased presentation of the data dependent on the willingness of people volunteering to submit the ADE report. Data indicating the specific type of Toxoplasmosis infection, specific dosages of the reported drugs and therapies being completed for possible comorbid conditions was not available in this study.

Francis et al., (2008) is by far the weakest study included in this review. This prospective study had a low N value, was unclear regarding consistency of methods among participants and was unclear regarding participant retention. Generalization of the results to the greater population is difficult due to unclear demographics studied and mention of missing confirmation of actual active Toxoplasmosis infection in some participants.

Current Gaps in Knowledge and Areas for Future Research

There continues to be a need for updated, current data that is more generalizable to larger populations. Many of the studies presented here utilized small sample sizes and were completed in remote areas of the world. Further studies looking at treatment dosages, durations, combinations and administration routes need to occur to identify the most effective treatment of active Toxoplasmosis infections with the smallest adverse side effect profile.

Conclusion

This literature review has shown trimethoprim-sulfamethoxazole can be an effective and safe treatment option for active Toxoplasmosis infection in some patient cases. Based on this literature review it is not clear if trimethoprim-sulfamethoxazole is more effective than the current gold standard treatment of pyrimethamine during the active stage of disease in all patient cases.

It is recommended future research occur to determine optimal treatment dosages, durations, drug combinations and drug administrations routes for the safest and most effective treatment of active Toxoplasmosis infections.

Application to Clinical Practice

As is true in most patient care management a unique and individualized approach is necessary for each patient case due to numerous variables. Based on this literature review, trimethoprim-sulfamethoxazole can be a safe and effective treatment option for certain patient cases of active Toxoplasmosis infection and should be considered when determining the best treatment option for the patient; whereas, other patient cases of active Toxoplasmosis infection may be more effectively and safely treated with the classic pyrimethamine combination therapy.

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