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Management of trichomoniasis in the setting of 5-nitroimidazole hypersensitivity

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Abstract

Metronidazole and other 5-nitroimidazoles are mainstays of *T. vaginalis* treatment, with few efficacious and safe treatment options available outside of this class. Patients with trichomoniasis and a history of a clinically confirmed hypersensitivity reaction to 5-nitroimidazoles present a management challenge for clinicians. The first step in managing such patients is metronidazole desensitization. In situations where this cannot be performed or tolerated, treatment with alternative regimens outside of the 5-nitroimidazole class, such as intravaginal boric acid or paromomycin, may be possible.

Short Summary

Patients with trichomoniasis and 5-nitroimidazole hypersensitivity present a difficult management challenge requiring either desensitization or alternative treatment regimens outside of this drug class.

Keywords

trichomoniasis; 5-nitroimidazole; metronidazole; allergy; sexually transmitted infections

Introduction

Trichomonas vaginalis is the most common, non-viral sexually transmitted infection (STI) worldwide.[1] Common symptoms include vaginal and penile discharge as well as dysuria;[2-4] however, *T. vaginalis* is often asymptomatic.[2] Untreated infection is associated with adverse birth outcomes and a 2-3 fold increased risk of HIV .[5,6] In addition, *T. vaginalis* has been associated with herpes simplex virus type 2 (HSV-2) shedding[7] and *T. vaginalis*-infected

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women have a higher incidence of HSV-2.[8] *T. vaginalis* has also been associated with the presence of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and human papillomavirus (HPV).[9,10]

Currently, the 2015 Centers for Disease Control and Prevention (CDC) STD Treatment Guidelines recommend treatment of *T. vaginalis* with metronidazole (MTZ) or tinidazole (TDZ) for women and men.[11] Both drugs are 5-nitroimidazoles with similar chemical structures but differing half-lives (MTZ 7-8 hours; TDZ 12-14 hours).[12] This similar structure results in cross-reactivity among drugs in the class, making treatment of *T. vaginalis* in patients with 5-nitroimidazole hypersensitivity difficult as there are limited treatment options outside of this class.[13] Multiple hypersensitivity reactions to MTZ have been reported, including Types I, II, and IV.[14] Most commonly, patients with 5-nitroimidazole hypersensitivity present with a Type I reaction in the form of urticaria, or hives.[15] Type I hypersensitivity reactions are immediate (i.e. occurring within 1-2 hours of offensive drug exposure) and mediated by drug-specific IgE antibodies, resulting in not only urticaria, but potentially serious and life-threatening manifestations such as angioedema, bronchospasm, and anaphylaxis.[16]

In this commentary, we review approaches to the management of *T. vaginalis* in the setting of 5-nitroimidazole hypersensitivity by discussing approaches to desensitization as well as alternative treatment regimens outside of the 5-nitroimidazole class.

Evaluation of reaction, graded oral challenge, and desensitization

The overwhelming majority of the literature regarding desensitization for 5-nitroimidazole hypersensitivity describes experiences with MTZ.[14,17,18] To our knowledge, there are no reports of IgE-mediated cross reactivity between MTZ and TDZ, but given that these drugs belong to the same class, cross reactivity is expected. More research in needed in this area as there are conflicting published reports. One case report describes a patient taking TDZ who presented with both anaphylaxis and Stevens-Johnson syndrome, but experienced no adverse effects while taking MTZ.[19] In contrast, there are several case reports describing cross reactivity between MTZ and TDZ and patients presenting with a fixed drug eruption, a Type IV hypersensitivity reaction.[13,20]

Although hypersensitivity intolerance prevalence (IgE and non-IgE mediated reactions) to MTZ has been found to be approximately 0.15%,[21] treatment of patients with trichomoniasis with these reactions is difficult. The first step in managing a patient in this setting is to verify the presence of a true hypersensitivity reaction through a careful history.[22] Obtaining history regarding the timing of the patient's previous reaction to MTZ is key as IgE-mediated reactions typically occur within 1-2 hours of offending drug exposure.[23] For patients with a questionable IgE-mediated allergic history to MTZ, skin prick testing could theoretically be done, although the overwhelming majority of validated data for this practice is with penicillin.[24] Thus, we do not recommend this practice for MTZ currently. However, a graded oral challenge (also known as a drug provocation test) could be considered. Graded oral challenge should only be performed for diagnostic purposes and only if the provider believes the patient is likely to pass the challenge based on his/her reported allergy history.

Importantly, graded oral challenges should be avoided in patients who report hypersensitivity symptoms that are not consistent with Type I reactions, which can manifest in severity, ranging from fixed drug eruptions to toxic epidermal necrolysis (TEN).[25]

Data are limited on optimal dosing regimens for graded oral challenges. Conventional oral drug challenges often include 3-4 incrementally increasing doses of the drug and can be performed in either the outpatient or inpatient setting.[26] Three step challenges typically start at 1/100th, then 1/10th, and then the remainder of the full dose.[21,27] One sample approach for MTZ would be to give 5 mg, followed by 50 mg, and then 445 mg to a total of 500 mg, with each dose separated by 30-60 minutes to ensure tolerance. These doses can be compounded by creating a suspension with MTZ in a vehicle such as cherry syrup.[28] Patients should be observed for 1-2 hours after the final dose. Patients with multiple reported drug allergies often report subjective symptoms during a graded oral challenge, which can be difficult to differentiate as true reactions. For these patients, referral to an allergist should be considered given their experience in clarifying reactions in such patients.[25]

Given the potential for a patient to experience anaphylaxis or other symptoms during a graded oral challenge, clinical staff should be trained to recognize associated symptoms and be ready to administer immediate treatment with intramuscular epinephrine, antihistamines, and corticosteroids, if indicated.[16] Monitoring during a graded oral challenge should include assessment of vital signs prior to starting the challenge. Nursing staff should check on the patient undergoing graded oral challenge every 10 to 15 minutes. If the patient develops any symptoms, vital signs should be repeated and the patient should be examined by a provider to determine if any treatment is needed. The ability to deliver inhaled bronchodilators would also be recommended, especially if the patient has underlying asthma. These challenges could be performed by a non-allergy specialist if appropriately monitored, but referral to an allergy specialist should also be considered.

Once an IgE-mediated reaction to MTZ has been confirmed, either by detailed history or graded oral challenge, MTZ desensitization should be considered. The first oral protocol for MTZ desensitization was published by Kurohara et al in 1991[18] and then modified in 2014 by Gendelman et al.[14] The modified oral protocol follows more closely with conventional desensitization protocols with a more gradual dosing regimen.[29] Depending on the severity of the initial reaction to the medication, conventional desensitization protocols start at 1/10,000th of the planned final dose. Depending on the route of administration, subsequent doses are increased every 15-30 minutes according to protocol, until the cumulative dose is equal to the planned final dose.[14] The first IV protocol (i.e. the Pearlman protocol, deemed an incremental dosing protocol) was published in 1996.[30] The Gendelman and Pearlman desensitization protocols are summarized in Table 1. Intensive monitoring is required during desensitization due to the need for frequent drug administration and close monitoring for reactions. Given these monitoring requirements, desensitization should not be performed in the outpatient setting and inpatient admission is recommended. ICU level care is often recommended for desensitization given the risk of reactions, including anaphylaxis, and the potential need for emergency care, but 1:1 nursing care on a step-down unit may also be appropriate. Coordination with a pharmacist regarding the protocol is necessary since repeated or added doses may need to be expedited. After successful completion of

desensitization, patients are able to safely take MTZ for 4-5 half lives of the drug, approximately 2 days. If the desensitization protocol is interrupted and/or the drug is not continued at regular intervals after completion of the protocol (4-5 half-lives of the drug), then the protocol will need to be restarted from the beginning.[21] For pregnant patients with trichomoniasis, desensitization is not recommended as the risks outweigh the benefits.[31]

To our knowledge, head-to-head studies of the relative safety of the IV and oral desensitization protocols have not been published.[16,32] However, one meta-analysis of published reports of IV and oral penicillin desensitization showed no statistical difference between reactions or success for either route.[33] A paper published by the CDC detailed 15 women who underwent MTZ desensitization protocols for treatment of *T. vaginalis*, eight of whom completed the Kurohora protocol and seven of whom the Pearlman protocol. One patient from each treatment group had mild symptoms during desensitization, which resolved with treatment. All were able to successfully complete the desensitization process and were cured of *T. vaginalis*.[35]

When considering IV versus oral desensitization, one route is not recommended over the other and recommendations must be tailored to each patient's individual case. There are no data to support choosing oral versus IV desensitization based on the severity of the reaction . One consideration of an IV desensitization regimen is that symptoms may develop more quickly in this setting resulting in increased risk of morbidity but medication administration can be stopped immediately should a reaction occur. Orally administered MTZ is absorbed more slowly than IV (peak absorption concentrations occur 1-2 hours after administration compared to immediate absorption with IV MTZ). The slower absorption of oral MTZ may allow for a slower course of reaction and therefore more time for treatment and evaluation. If there are concerns that a patient may experience gut malabsorption (i.e. in the setting of ileus or bowel obstruction), the IV MTZ desensitization route should be considered over the oral route.

Alternative treatment regimens in the event desensitization cannot be performed or is not tolerated

Because 5-nitroimidazoles are the only drug class currently recommended for treatment of *T. vaginalis*, use of alternative regimens outside of this class is largely based on anecdotal evidence and expert opinion.[11] In the setting of true IgE-mediated MTZ hypersensitivity, other 5-nitroimidazoles, including TDZ, should be avoided because of cross reactivity.[13] Secnidazole (SEC) is another 5-nitroimidazole with trichomoncidal activity[34] that, interestingly, in one case report, did not exhibit cross-reactivity with MTZ or TDZ.[35] While SEC could be an alternative to MTZ or TDZ for treatment of trichomonas in patients with IgE-mediated 5-nitroimidazole hypersensitivity, the data are too limited at this time to recommend this practice, as the risks of a potential serious reaction outweigh the benefits of administration. Intravaginal formulations of TDZ and MTZ are also commercially available. Intra-vaginalMTZ has been used in combination with miconazole to successfully treat trichomoniasis in women.[36] This intra-vaginal treatment could be useful in women unable to tolerate oral 5-nitroimidazoles due to adverse systemic effects such as gastrointestinal

complaints. However, the study in which this treatment regimen was given excluded women with 5-nitroimidzole allergy. eWe are currently not aware of any data that demonstrate that it is safe to give intra-vaginal preparations to women with 5-nitroimidazole hypersensitivity and do not recommend use of these medications in this setting.

Table 2 summarizes the data for alternative treatment regimens outside of the 5-nitroimidazole class based on our review of the medical literature. We searched PubMed and EMBASE for papers detailing management of patients with trichomoniasis in the setting of MTZ allergy using the search terms “trichomoniasis AND metronidazole AND allergy AND treatment” and “trichomoniasis AND metronidazole AND hypersensitivity AND treatment.” Abstracts of articles were read and references cited in order to ascertain which articles included use of alternative treatment regimens in patient care. In the event that desensitization fails or cannot be performed, there are several intra-vaginal regimens which have been occasionally reported as effective in the literature[37–43], but no acceptable systemic therapies have been reported to date. It is important to note that intra-vaginal medications may not reach all sites infected with *T. vaginalis* (i.e. Bartholin’s and Skene’s glands) as effectively as systemic medications.[40] These medications may have to be compounded at a pharmacy (i.e. intra-vaginal paromomycin) when not commercially available, and their cost is also higher than that of MTZ. In addition, they require a prolonged course of therapy and patient compliance may become an issue. There can also be adverse side effects locally, in the vaginal canal, due to topical therapies. Because of these issues, referral to an allergist for potential desensitization is the recommended first step in management of a *T. vaginalis*-infected patient with 5-nitroimidazole hypersensitivity.[11]

Intra-vaginal boric acid has been shown to demonstrate trichomonicidal activity *in vitro*[44] by acidifying the vaginal environment, leading to inactivation of factors that contribute to *T. vaginalis* pathogenicity, such as cell-detaching factor.[45–47] Several case reports have noted efficacy in treating patients with 5-nitroimidazole allergy with intravaginal boric acid 600mg capsules twice daily, either alone or in conjunction with other agents such as intra-vaginal clotrimazole, for at least 60 days, leading to both symptomatic and microbiological cure.[38,40,42] This medication is generally well tolerated.[48]

Paromomycin is an aminoglycoside that has to be compounded for intravaginal administration to treat trichomoniasis in the setting of 5-nitroimidazole hypersensitivity.[49] Regimens of intravaginal paromomycin 6.25% cream for 8 to 14 days have resulted in symptomatic and microbiological cure in several case reports and case series.[37,39,41,43] Intravaginal administration of paromomycin can result in painful vulvar ulcers acutely, but these are self-limited and resolve once treatment is complete.[50] Application of lubricating jelly to the vulva prior to administration of intravaginal paromomycin has been successful in preventing the development of ulcers in some patients.[41] Betadine douches and intravaginal clotrimazole have also demonstrated symptomatic and microbiological cure for some patients, though data for these are more limited than intra-vaginal boric acid and paromomycin.[39]

Auranofin, an anti-rheumatic drug composed of gold particles in capsule form, has shown potential as an oral alternative to 5-nitrominidazoles for treatment of *T. vaginalis* in a mouse

model of vaginal infection.[51] This moiety works by inactivating the thioreductase enzyme in the *T. vaginalis* parasite, therefore impeding it from overcoming oxidant stress. In murine studies, oral administration of this drug cleared *T. foetus* after 4 days. However, additional research is needed to ascertain the efficacy and safety of this medication in humans.

Conclusion

Although 5-nitroimidazole hypersensitivity is rare, it can complicate the management of some patients with trichomoniasis. Treatment options for patients with true 5-nitroimidazole hypersensitivity reactions are limited to oral or IV desensitization or, if desensitization fails or cannot be performed, alternative intra-vaginal treatments with limited efficacy data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Rowley J, Vander Hoorn S, Korenromp E, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. Bull World Health Organ 2019;97:548–62p. [PubMed: 31384073]
2. Meites E, Gaydos CA, Hobbs MM, et al. A Review of Evidence-Based Care of Symptomatic Trichomoniasis and Asymptomatic Trichomonas vaginalis Infections. Clin Infect Dis 2015;61:S837–S48. [PubMed: 26602621]
3. Committee on Practice B-G. Vaginitis in Nonpregnant Patients: ACOG Practice Bulletin, Number 215. Obst Gynecol 2020;135:e1–e17. [PubMed: 31856123]
4. Krieger JN, Verdon M, Seigal N, et al. Natural History of urogenital trichomoniasis in men. J Urol 1993;149:1455–8. [PubMed: 8501787]
5. Silver BJ, Guy RJ, Kaldor JM, et al. Trichomonas vaginalis as a cause of perinatal morbidity: a systematic review and meta-analysis. Sex Transm Dis 2014;41:369–76. [PubMed: 24825333]
6. McClelland RS, Sangaré L, Hassan WM, et al. Infection with Trichomonas vaginalis Increases the Risk of HIV-1 Acquisition. J Infect Dis 2007;195:698–702. [PubMed: 17262712]
7. Boselli F, Chiossi G, Bortolamasi M, et al. Prevalence and determinants of genital shedding of herpes simplex virus among women attending Italian colposcopy clinics. Eur J Obstet Gynecol Reprod Biol 2005;118:86–90. [PubMed: 15596279]
8. Gottlieb SL, Douglas JM Jr., Foster M, et al. Incidence of herpes simplex virus type 2 infection in 5 sexually transmitted disease (STD) clinics and the effect of HIV/STD risk-reduction counseling. J Infect Dis 2004;190:1059–67. [PubMed: 15319854]
9. Ginocchio CC, Chapin K, Smith JS, et al. Prevalence of Trichomonas vaginalis and coinfection with Chlamydia trachomatis and Neisseria gonorrhoeae in the United States as determined by the Aptima

Trichomonas vaginalis nucleic acid amplification assay. J Clin Microbiol 2012;50:2601–8. [PubMed: 22622447]

10. Lazenby GB, Taylor PT, Badman BS, et al. An association between Trichomonas vaginalis and high-risk human papillomavirus in rural Tanzanian women undergoing cervical cancer screening. Clin Ther 2014;36:38–45. [PubMed: 24417784]
11. Workowski KA. Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. Clin Infect Dis 2015;61 Suppl 8:S759–62. [PubMed: 26602614]
12. Edwards DI. Nitroimidazole drugs-action and resistance mechanisms I. Mechanism of action. J Antimicrob Chemother 1993;31:9–20.
13. Mishra D, Mobashir M, Zaheer MS. Fixed drug eruption and cross-reactivity between tinidazole and metronidazole. Int J Dermatol 1990;29:740. [PubMed: 2148563]
14. Gendelman SR, Pien LC, Gutta RC, et al. Modified oral metronidazole desensitization protocol. Allergy Rhinol (Providence) 2014;5(2):66–9. [PubMed: 24612959]
15. García-Rubio I, Martínez-Cócera C, Santos Magadán S, Rodríguez-Jiménez B, Vázquez-Cortés S. Hypersensitivity reactions to metronidazole. Allergol Immunopathol (Madr) 2006;34:70–2. [PubMed: 16606549]
16. Khan D Drug Allergy. In: Adelman D, ed. Manual of Allergy and Immunology. Philadelphia, Pennsylvania: Lippincott, Williams, & Wilkins; 2012:286–486.
17. Yung CC, Watts TJ, Haque R. Successful desensitization to metronidazole in a patient with generalized fixed drug eruption. J Allergy Clin Immunol Pract 2020;8:769–71.e1. [PubMed: 31369825]
18. Kurohara ML, Kwong FK, Lebherz TB, et al. Metronidazole hypersensitivity and oral desensitization. J Allergy Clin Immunol 1991;88:279–80. [PubMed: 1880329]
19. Singbal SS, Rataboli PV. Anaphylaxis and hypersensitivity syndrome reactions in increasing severity following repeated exposure to tinidazole. J Postgrad Med 2005;51:243–4. [PubMed: 16333209]
20. Kanwar AJ, Sharma R, Rajagopalan M, et al. Fixed drug eruption due to tinidazole with cross-reactivity with metronidazole. Dermatologica 1990;180:277. [PubMed: 2141581]
21. Macy E, Romano A, Khan D. Practical Management of Antibiotic Hypersensitivity in 2017. J Allergy Clin Immunol Pract 2017;5:577–86. [PubMed: 28365277]
22. Trubiano JA, Vogrin S, Chua KYL, et al. Development and Validation of a Penicillin Allergy Clinical Decision Rule. JAMA Intern Med 2020;180:745–52. [PubMed: 32176248]
23. Brockow K, Przybilla B, Aberer W, et al. Guideline for the diagnosis of drug hypersensitivity reactions: S2K-Guideline of the German Society for Allergology and Clinical Immunology (DGAKI) and the German Dermatological Society (DDG) in collaboration with the Association of German Allergologists (AeDA), the German Society for Pediatric Allergology and Environmental Medicine (GPA), the German Contact Dermatitis Research Group (DKG), the Swiss Society for Allergy and Immunology (SGAI), the Austrian Society for Allergology and Immunology (ÖGAI), the German Academy of Allergology and Environmental Medicine (DAAU), the German Center for Documentation of Severe Skin Reactions and the German Federal Institute for Drugs and Medical Products (BfArM). Allergo journal international 2015;24:94–105. [PubMed: 26120552]
24. Sogn DD, Evans R 3rd, Shepherd GM, et al. Results of the National Institute of Allergy and Infectious Diseases Collaborative Clinical Trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. Arch Int Med 1992;152(5):1025–32. [PubMed: 1580706]
25. Aberer W, Bircher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy 2003;58(9):854–63. [PubMed: 12911412]
26. Warrington R, Silviu-Dan, Wong T. Drug Allergy. Allergy Asthma Clin Immunol 2018;14 (Suppl 2):60. [PubMed: 30275849]
27. Khan DA, Solensky R. Drug allergy. J Allergy Clin Immunol 2010;125:S126–37. [PubMed: 20176256]

28. Allen LV, Erickson MA. Stability of ketoconazole, metolazone, metronidazole, procainamide hydrochloride, and spironolactone in extemporaneously compounded oral liquids. Am J Health Syst Pharm 1996;53:2073–8. [PubMed: 8870895]

29. Cernadas JR, Brockow K, Romano, et al. General considerations on rapid desensitization for drug hypersensitivity - a consensus statement. Allergy 2010;65:1357–66. [PubMed: 20716314]

30. Pearlman MD, Yashar C, Ernst S, et al. An incremental dosing protocol for women with severe vaginal trichomoniasis and adverse reaction to metronidazole. Am J Obstet Gynecol 1996;174:934–6. [PubMed: 8633672]

Table 1.

Protocols for metronidazole desensitization in the setting of 5-nitroimidazole hypersensitivity

Modified Kurohara Protocol[14] (PO)[a]	**Pearlman Protocol[30] (IV, PO)**
Dose 1, 0.0025 mg	Dose 1, 0.005 mg[b]
Dose 2, 0.025 mg	Dose 2, 0.015 mg
Dose 3, 0.25 mg	Dose 3, 0.05 mg
Dose 4, 2.5 mg	Dose 4, 0.15 mg
Dose 5, 5 mg	Dose 5, 0.5 mg
Dose 6, 10 mg	Dose 6, 1.5 mg
Dose 7, 25 mg	Dose 7, 5 mg
Dose 8, 50 mg	Dose 8, 15 mg
Dose 9, 100 mg	Dose 9, 30 mg
Dose 10, 250 mg	Dose 10, 60 mg
Dose 11, 500 mg	Dose 11, 125 mg
Dose 12, 1000 mg	Dose 12, 250 mg[c]
	Dose 13, 500 mg
	Dose 14, 2000 mg

[a] PO doses in the Modified Kurohara Protocol are administered 30 minutes apart

[b] Start of IV dosing, administered 15-20 minutes apart

[c] Start of PO dosing, administered 60 minutes apart

Abbreviations: IV, intravenous; mg, milligram; PO, oral

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Table 2.

Evidence for alternative treatment regimens outside of the 5-nitroimidazole drug class for *T. vaginalis*-infected patients with 5-nitroimidazole hypersensitivity

Authors/DatePublished	Case Presentation	Treatment (Duration)	Outcome	Follow-Up
Nyirjesy, et al.[37](1998)	9 women total[a], 5 with hypersensitivity to MTZ	Intravaginal paromomycin 250mg per 4g applicator QD (2 weeks)	9 of 9 symptomatic cure[b]	4-6 weeks post treatment
Aggarwal, et al.[38](2008)	58-year-old woman with Type I hypersensitivity to MTZ	Intravaginal clotrimazole daily alternating nightly with intravaginal boric acid 600mg capsules (5 months)	Symptomatic and microbiological (culture) cure	Timeframe of TOC not specified
Helms, et al.[39](2008)	17 women with 5-nitroimidazole hypersensitivity	Betadine douches[c] Intravaginal paromomycin[c] Intravaginal clotrimazole[c] Intravaginal furazolidone Intravaginal acetarsol	Symptomatic and microbiological cure[d] in: 3 of 4 with Betadine douches 1 of 4 with intra-vaginal paromomycin 1 of 3 with intra-vaginal clotrimazole 0 of 2 with intra-vaginal furazolidone[e] 0 of 1 with intra-vaginal acetarsol	Timeframe of TOC not specified
Muzny, et al.[40](2012)	37-year-old black woman Type I hypersensitivity to MTZ	Intravaginal boric acid 600mg capsules BID (2 months)	Symptomatic and microbiological (wet mount and culture) cure	TOC 60 days post end of treatment
Keating, et al.[41](2015)	Woman with severe 5-nitroimidazole allergy	Intravaginal paromomycin 6.25% cream, 5g daily (14 days)	Symptomatic and microbiological (OSOM® rapid test, NAAT, or culture) cure	Timeframe of TOC not specified
Backus, et al.[42] (2017)	67-year-old white woman with Type I hypersensitivity to MTZ	Intravaginal boric acid 600mg capsules BID (60 days)	Symptomatic and microbiological (NAAT) cure	Timeframe of TOC not specified
Thomas, et al.[43] (2018)	27-year-old woman with Type I hypersensitivity to MTZ	Intravaginal paromomycin 6.25% BID (8 days)	Symptomatic and microbiological (wet mount and culture) cure	26 days post end of treatment

[a] Results did not differentiate between MTZ resistant and hypersensitive patients

[b] 8 of 9 women had negative wet mounts and 6 of those 8 had negative *T. vaginalis* cultures. One patient with a negative culture relapsed within 4 weeks of treatment

[c] Dose and duration of treatment were not specified and varied amongst patients

[d] Follow-up data available for 12 of 17 patients

[e] One of these two patients was subsequently cured with betadine douches (dose and duration not specified)

Abbreviations: BID, twice daily; MTZ, metronidazole; NAAT, nucleic acid amplification test; PO, orally; QD, daily; TOC, test of cure