Therapy for Whipple’s disease

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Whipple’s disease was first described in 1907, the genomic composition of the causative organism, Tropheryma whipplei, was unravelled in 2003 and its in vitro susceptibility to antibiotics started to be explored in 2004–05. Still today, this knowledge is not fully applied in the recommendations for the therapy of this disease. In this paper, we summarize the current recommendations on antimicrobial therapy for Whipple’s disease and propose a shift in the maintenance therapy.

Keywords: Tropheryma whipplei, sulphonamides, trimethoprim, antimicrobial therapy

Introduction

Current recommendations for the therapy of Whipple’s disease are still not based on therapeutic trials or on the knowledge of the genomic composition of Tropheryma whipplei. They are rather based on case reports and retrospective case series, pharmacokinetic data on antimicrobial agents and preliminary data from in vitro susceptibility testing studies. Standard recommendations encompass the oral administration of 160 mg of trimethoprim and 800 mg of sulfamethoxazole twice daily for 1 or 2 years, usually preceded by parenteral administration of ceftriaxone (2 g daily) or streptomycin together with penicillin G (2 g and 1.2 million U daily, respectively) for 2 weeks.1 The European Network on T. whipplei infections (see http://www.eurice.info/typo3sites/index.php?id=167&L=2) recently completed the first prospective trial comparing parenteral meropenem (3 g daily) with ceftriaxone (2 g daily) for the first 2 weeks of therapy, followed by the standard maintenance with oral trimethoprim/sulfamethoxazole for 1 year in 40 patients.2 All the above-mentioned antimicrobial agents have a good penetration in the central nervous system. This is highly desirable in Whipple’s disease since neurological involvement is common and has a poor prognosis. Previous studies have shown that, even using the recommended maintenance therapy, lack of response and relapses are possible. Moreover, the optimal duration of the maintenance therapy is also unclear; 2 year maintenance with antimicrobial agents is not enough to prevent relapses in some patients, whereas 1 year will suffice in others.1,3–6

Trimethoprim/sulfamethoxazole

Trimethoprim and sulfamethoxazole are antimetabolites that interfere with the synthesis of folic (pteroylglutamic) acid. The structural components of the latter are p-aminobenzoic acid (PABA), pteridine and glutamate. Sulphonamides (sulfadiazine, sulfizoxazole and sulfamethoxazole) compete with PABA as substrates for the enzyme dihydropteroic acid synthetase (DHPS), which adds PABA to pteridine. The selective effect of sulphonamides on bacteria is due to the fact that these synthesize folic acid and possess the gene that encodes for DHPS, whereas mammalian cells do not and are therefore dependent on exogenous folic acid supplies.

Trimethoprim and also pyrimethamine are structural analogues of pteridine and competitive inhibitors of dihydrofolate reductase (DHFR), which reduces dihydrofolate acid to tetrahydrofolic acid. Compared with the mammalian enzyme, bacterial DHFR has 1000-fold greater sensitivity to trimethoprim, which explains the selectivity of this agent.

The rationale for the combination of trimethoprim and sulfamethoxazole (co-trimoxazole) or sulfadiazine with pyrimethamine is to achieve synergy by inhibition in two sequential enzymes in the folic acid pathway. This could result in maintained or increased efficacy even at lower doses of the drugs, and thus reduce toxicity.7 The use of the above-mentioned combinations can also reduce the occurrence of acquired bacterial resistance. This is the reason why monotherapy with sulphonamides is rare nowadays.

The most prevalent mechanism of acquired resistance to sulphonamides and trimethoprim is the acquisition of mutations in the target genes that encode DHPS and DHFR. This has been well documented in many infectious agents including Plasmodium falciparum, Pneumocystis jirovecii, Toxoplasma gondii, Enterococcus faecalis and Campylobacter jejuni. The activity of sulphonamides can also be reduced by a secondary increase in DHFR levels or activity or by the presence of excess PABA or exogenous thymidine and purines. Like the sulphonamides, trimethoprim is bactericidal, but is only bacteriostatic in...
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the presence of an excess of thymidine. Such an excess can occur in some infections as a result of cell breakdown. Relapses of Whipple’s disease1,3,4 and acquired resistance to trimethoprim/sulfamethoxazole6 have been documented although the mechanisms that play a role in this are not yet known. Natural resistance to sulphonamides and trimethoprim may be due to the lack of the target enzyme (DHPS and DHFR, respectively).

Spurs to review T. whipplei therapy

In 2003, the genomic analysis of T. whipplei showed that the microorganism lacks the coding sequence for DHFR, which is the target for trimethoprim.8 This finding has been confirmed in cell cultures and axenic medium, which demonstrated that the in vitro activity of trimethoprim/sulfamethoxazole is due to sulfamethoxazole alone.9,10 It must be pointed out that these data are preliminary. It is very difficult to culture T. whipplei; the already mentioned in vitro susceptibility testing studies were performed at a single laboratory (Dr Raoult, Faculté de Médecine, Université de la Méditerranée, Marseille) and need to be reproduced by others. Using cell cultures, the same group also demonstrated that the combination of doxycycline with hydroxychloroquine, as alkalinizing agent, was bactericidal for T. whipplei. Such a combination had been previously successful in vitro for Coxiella burnetii and Staphylococcus aureus, organisms that also reside in acidic vacuoles.10

Time for a change?

In a recent review on Whipple’s disease and based on these studies, the authors have suggested a long-term regimen of doxycycline and hydroxychloroquine for the eradication of intra-cellular organisms in patients without neurological involvement and to add a high dose of sulfamethoxazole or sulfadiazine only in patients with neurological involvement. Lack of neurological involvement in this study is defined as a negative PCR assay of CSF and the absence of neurological symptoms.1

A combined regime of doxycycline and hydroxychloroquine has been successful in the treatment of Q fever endocarditis caused by C. burnetii and preliminary observations by Fenollar et al.1 in four unpublished cases suggest that this may also be true in Whipple’s disease.

Nevertheless, doxycycline and other tetracyclines do not cross the blood–brain barrier and hydroxychloroquine accumulates in the CNS to a lesser extent than in other organs. Moreover, absence of neurological symptoms and a negative PCR of CSF does not fully exclude involvement of the CNS in Whipple’s disease.

Neurological and other considerations

In view of the relatively high rate of initial neurological involvement, the use of doxycycline and hydroxychloroquine alone, as standard first-line therapy, may be very problematic, although it might be worth trying in combination with standard antimicrobial recommendations. It is also clear that maintenance therapy needs to be improved in view of the frequent relapses despite specific antibiotic therapy (2% to 33% after an average of 5 years), the fact that relapse is often characterized by neurological involvement and the poor prognosis in those patients.3,4 The lesson to be learned from the genomic analysis and from the in vitro tests of T. whipplei is that trimethoprim may not be necessary in the therapy for Whipple’s disease. We would therefore suggest that, after the initial 2 weeks of parenteral antibiotic treatment with ceftriaxone or streptomycin together with penicillin, a high-dose regimen of sulphonamide alone should be tried in a limited number of patients. Ideally, if the results of this pilot are positive, a prospective study comparing maintenance therapy with trimethoprim/sulfamethoxazole with high-dose sulphonamide should be performed thereafter. Considering the rarity of the disease and the slow recruitment achieved in the recent European study,2 this would require a worldwide effort.

Transparency declarations

None to declare.

References