A combination of trimethoprim/sulfamethoxazole with linezolid is useful for actinomycotic mycetoma: A summary of the existing data and the rationale of combination therapy

Sir,

We read with interest the case by Patra *et al*.[1] and would like to highlight the dosing that we had used predating this case.[2] We would like to dwell on the laid down principles that dictate usage of antibiotics to effect clinical cure in actinomycotic mycetoma.

Antibiotic dosages are determined using susceptibility data, pharmacodynamics and treatment outcomes. Important considerations before instituting treatment include: (1) Region to region variation of antibiotic susceptibility patterns that are constantly changing; (2) the concentration of antibiotic attained at the site of infection over a dosing interval of 24 hours; (3) mechanism of antibacterial action of antibiotics; (4) the likelihood of the dose producing a microbiological as well as clinical cure; (5) the adverse effects that occur; and, (6) the probability of development of antimicrobial resistance. Pharmacodynamic descriptions provide the clinician with information on how the bacterial pathogens are killed. These parameters include %T>MIC, AUC: MIC or Cmax: MIC, where T is time, MIC is minimum inhibitory concentration, AUC is area under curve and Cmax is the maximum concentration. These parameters help to achieve the "antibiotic exposure break point" that can enable a proper dosage schedule. In the absence of this, guidance provided by the "break point organizations" such as the United States Committee on Antimicrobial Susceptibility Testing (www.uscast.org) or the Clinical and Laboratory Standards Institute Subcommittee on Antimicrobial Susceptibility Testing (https://clsi.org/education/microbiology/ast) can be used.

In our cases,[2] we confirmed *Nocardia* by culture and used existing microbiological data gleaned from the prevalent worldwide data, using the laid down principles of therapy. We found the need to synergise the use of trimethoprim-sulfametoxazole (TMP/SMX) and linezolid as the existing data in this condition relied on at least two drugs. Our data showed that a regimen of linezolid 600 mg twice a day for three months along with TMP/SMX (sulfamethoxazole 1200 mg and trimethoprim 240 mg) for six months led to remission in three out of four cases.[2] Mean time in which the lesion healed was three months. Previously, Welsch *et al*.[3] and Epelboin *et al*.[4] have also reported use of linezolid in the specific management of actinomycotic mycetoma.

Here it is pertinent to note that we felt the need to combine these two drugs but in the case by Patra *et al*.,[1] we did not note any data on culture or antibiogram. While authors administered monotherapy, this may not have been justified unless resistance had been documented to all the previously used drugs. We fear a single drug may predispose the patient to resistance and recurrence.

There are three general settings, elaborated as follows, in which combination antimicrobial therapy is known to be advantageous. The first is in the empirical setting, when treating an infection for which the potential etiologic microbial species are sufficiently broad so that one agent is unlikely to cover all of them. The second is for preventing the emergence of resistance in specific clinical settings. The third is a rare circumstance in which two active agents are known to result in superior clinical outcomes compared with a single active agent against a susceptible organism.[5] In actinomycotic mycetoma, when the correct species is not identified, it makes logical sense to combine two classes of drugs. It has been our experience that using TMP/SPX with linezolid is effective with long term results obviating the risk of resistance. Also, long-term linezolid can lead to haematological side effects which need monitoring, which was not mentioned in the report by Patra *et al*.[1]

There is an additional advantage of using two oral drugs; it obviates the need for parenteral administration of aminoglycosides. But any such use should be based on an antibiogram. Drug monotherapy should not be the preferred

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line of treatment, according to the existing principles of antibiotic use.[5]

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Authors' Reply

Sir,

We thank the correspondents[1] for their interest in our article.[2] We apologise for missing their article in our review of literature. While we agree with their comments, we could not plan treatment for our patient based on drug sensitivity as the organism did not grow in culture. We used empirical monotherapy with linezolid because she had failed combination treatment with amikacin, cotrimoxazole and doxycycline. The patient has not shown any recurrence after two years of follow-up.

Declaration of patient consent

The patient's consent is not required as the patient's identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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