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Current Trachoma Treatment Methodologies

Focus on Advancements in Drug Therapy

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Abstract

Currently, there are approximately 6 million people with irreversible blindness as a result of chronic follicular conjunctivitis with subsequent corneal scarring caused by *Chlamydia trachomatis,* also known as trachoma. On the basis of the clinical studies evaluated, the most widely tested effective pharmacological treatments for trachoma today are topical tetracycline 1% to be applied to both eyes twice daily for 6 weeks or a single oral dose of azithromycin 20 mg/kg (up to 1g). Although chemotherapy can generate prompt therapeutic response and surgery can reverse the repercussions of these infections, these conditions will persist through reinfections. Implementing proper personal hygiene and environmental improvement measures for the control of infection transmission will be essential in reducing the potentially devastating results of trachoma infections.

As one of the oldest infections known to mankind, trachoma was first documented in the pharaonic era in Egypt.[1] Although understood to be a chronic follicular conjunctivitis condition caused by *Chlamydia trachomatis* that is susceptible to several classes of antibacterials, it remains the leading cause of preventable blindness worldwide.[2] Currently, there are approximately 6 million people with irreversible blindness as a result of trachoma; furthermore, an estimated 150 million patients with active disease require treatment in order to prevent this potential consequence.[1,3] It is important to keep in mind that this apparently ancient disease can have a considerable impact on this generation because the majority of the infected are paediatric patients. Since the ramification of this condition bears such a significant yet preventable outcome, the World Health Organization (WHO) has developed an alliance to spearhead the elimination of trachoma globally by the year 2020 (GET 2020).[4-7] Other groups have joined in on this mission to support the WHO alliance, such as the International Trachoma Initiative (ITI) formed by the Edna McConnell Clark Foundation and Pfizer Inc., and to work with national programmes in a small group of countries to expand trachoma control.

By adopting a comprehensive set of control measures for trachoma in endemic areas, the following measures (identified by the acronym 'SAFE') have been implemented: *S*urgery for trichiasis to correct for the in-turned eyelashes; *A*ntibiotics for infectious trachoma; *F*ace washing to reduce transmission; and *E*nvironmental improvement through advances in access to clean water and the control of disease spreading flies.[8-10] A literature search using the terms trachoma, tetracycline, azithromycin, erythromycin and doxycycline as well as a

review of the Cochrane database and WHO website lead to the review and selection of studies that allowed the authors to summarise current treatment methodologies and the science behind proving them when appropriate.

1. Trachoma Pathogenesis and Epidemiology

To understand the challenges that healthcare providers need to overcome in the process of eliminating trachoma, it is important to first examine the condition that is being dealt with. Trachoma conjunctivitis is caused by *C. trachomatis* (serotypes A, B, Ba or C) and is a chronic infection of the eye.[11,12] The disease is marked by follicular reaction in the superior tarsal conjunctiva that is frequently associated with a concurrent papillary response.[13] As the inflammatory response in the follicles resolve, fine subconjunctival scars begin to replace these structures. As the condition progresses, however, corneal involvement, including the development of a superior limbic pannus with opacification of the corneal stroma and neovascularisation, may occur. Often, the formation of these scars contributes to the distortion of the tarsal plate leading to in-turned eyelashes, also known as trichiasis, which abrade the cornea. Such constant irritation results in ulceration, scarring and, eventually, vision loss.[14] Currently, it is felt that the amount of scarring is related to the intensity of the follicular response as only repeated, severe disease appears to predispose the patient to blindness.[6] It is for this reason that appreciable scarring of the conjunctivae and corneas do not appear until well into the patient's adult life despite many initial infections that began in childhood.

Trachoma is identified commonly in large regions of Africa, the Middle East, Southwest Asia, the Indian subcontinent, the Aboriginal communities of Australia, and focal populations of Central and South America. It is undoubtedly a disease of poverty regardless of geographical region. This point has been proven over time, as there has been a strong historical connection between improvement in socioeconomic factors and the disappearance of endemic trachoma.[14]

The SAFE strategy addresses not only the short-term treatment options but also the importance of long-term prevention measures such as infection control. Since the disease transmission in endemic areas is through both direct and indirect hand-to-eye contact, one can imagine that hygiene factors, especially facial cleanliness and reduction of household flies, are essential parameters in the management of trachoma. Other common daily-living events that predispose to infection transmission include coughing and sneezing, and the sharing of bedding, handkerchiefs and towels.[15] Although the WHO recommended treatments are effective, measures to limit the rate of reinfection remains a significant component that can limit the success of the GET 2020 international alliance efforts if not equally utilised.[4]

2. Treatment Strategies

2.1 Surgery

Although the recurrence of infection is not able to be prevented by surgery, a large percentage of trachomatous blindness could be prevented by the pursuit of more timely trichiasis surgery.[16] The lack of trained ophthalmologists is not such an obstacle to a region as general practitioners or other medical personnel can be trained to perform the procedure appropriately.[17] The use of otherwise helpful procedures, such as corneal transplantation, for advanced disease are often impossible, mainly because of the extent of eye involvement from the infection, including entropion, keratinisation, and poor mucin and tear production.[6] For these reasons, preventing future chlamydial infections along with trichiasis surgery, thus become the most useful measures for eliminating the permanent long-term repercussions of trachoma.

2.2 Medication

An evidenced based medicine approach review of the current treatment strategies for trachoma has recently been published by the Cochrane Data-

Table I. Topical and oral treatment regimens for trachoma[13,14]

Route	Medication	Dosage
Topical	Tetracycline 1% ointment	Apply twice daily to both eyes for 6 weeks
Topical	Tetracycline 1% ointment	Apply daily to both eyes for 6 weeks
Topical	Oxytetracycline/polymyxin	Apply daily for 5 days every 4 weeks for 6 treatment cycles
Topical	Oxytetracycline/polymyxin	Apply twice daily for 8 weeks
Oral	Azithromycin	Single-dose 20mg/kg (up to 1g)
Oral	Azithromycin	One dose weekly for 3 weeks
Oral	Azithromycin	One dose every 4 weeks for 6 doses
Oral	Azithromycin	10mg/kg daily for 3 doses
Oral	Erythromycin	Based on adult dose 250mg four times daily for 2 weeks, adjusted per kg bodyweight for children with severe trachoma assigned to topical tetracycline arm
Oral	Erythromycin	250mg four times daily or 500mg twice daily for 14 days for women of childbearing age
Oral	Doxycycline	100mg twice daily x 14 days – avoid in children, pregnancy and breast feeding
Oral	Amoxicillin	500mg three times daily x 14 days for women of childbearing age with erythromycin intolerance

base,[18] however, the following review provides representative samples of recent trials to support the use of the various trachoma treatment modalities. Until recently, the mainstay approach to trachoma treatment has been the prolonged topical application of tetracycline ointment or the use of oral erythromycin or doxycycline (see table I).[2] However, because of the discomfort and blurred vision that result from the topical treatments,[11] along with the necessities of proper application techniques and 6-week regimen durations, patient compliance can often be less than optimal. Compliance is often also complicated with the erythromycin regimens because of the high incidence of gastrointestinal adverse effects. Despite the activity of oral doxycycline against *C. trachomatis*, its systemic administration has been associated with permanent discolouration of the teeth during childhood development.[19] One of the advanced generation macrolides, azithromycin, has been demonstrated to be an effective single-dose regimen as a result of its prolonged half-life and has the potential to virtually eliminate the compliance issues often associated with the topical ophthalmic regimens. As it has a proven safety profile in the paediatric population that is key to treating in the SAFE initiatives, and is far better tolerated than oral erythromycin, this oral option as well as topical tetracycline have become WHO first-line treatment options.

Although the effectiveness of both the oral and topical treatment regimens is comparable, it has been observed that lower recurrence rates may be achieved with the administration of systemic antibacterials.[11,20] This is because of the suspicion that recurrence may be reflective of chlamydial infection that is not limited to the eyes of children with trachoma, but is also present in their nasopharynx and rectum.[11,21] For this reason, topical antibacterial therapy may thus prove inadequate because the remaining reservoirs of infection are not eradicated and may indirectly promote reinfection of the disease.

As one of the first steps in assessing the utility of azithromycin for trachoma, the ocular pharmacokinetics of azithromycin were evaluated. Karcioglu and colleagues characterised and compared tear and serum concentrations of azithromycin in 13 school-age children with active trachoma after a single 20 mg/kg dose of oral azithromycin.[22] Peak tear and serum concentrations of 1.53 and 0.153 mg/L, respectively, were achieved within 12 hours of dose administration and then subsequently declined gradually in both sites over the course of the following 6 days. At the day 6 measurement, tear concentrations remained detectable at a concentration of 0.21 mg/L,

which indicates that they exceeded the average minimum inhibitory concentration (MIC) of 0.03–0.25 mg/L for *C. trachomatis*.[22] In a second study, Tabbara et al. characterised the penetration of azithromycin into tear fluid, aqueous humour and conjunctival tissue specimens in 60 patients undergoing cataract surgery.[23] Patients received a single 1g dose of oral azithromycin and had serum, aqueous and tear specimens collected for up to 4 days after azithromycin administration, while conjunctival tissue biopsy specimens continued to be collected for up to 14 days. Resulting documented concentration ranges were as follows: serum 0.021–0.974 mg/L; tears 0.082–2.892 mg/L; aqueous humour 0.01–0.07 mg/L; and conjunctival tissue 0.7–32 μg/g. The authors appropriately reported that the detected concentrations in tears and conjunctival tissue after 4 and 14 days, respectively, exceeded the MIC_{90} (minimum concentration to inhibit growth of 90% of isolates) of *C. trachomatis* following the single oral 1g dose of azithromycin. However, since the study population were undergoing cataract surgery rather than being treated for an active ocular infection it is possible the concentrations in the tissues/fluids of a patient with trachoma may be even higher as a result of the significant dependence on inflammation for azithromycin delivery.[21,24]

In an interestingly designed, targeted treatment study by Bowman et al., the efficacy of topical tetracycline (applied once by nurse in front of the caregiver, then twice daily by the caregiver for 6 weeks) was compared to that of oral azithromycin 20 mg/kg in an unsupervised environment in children from 6 months to 10 years of age.[25] This study design was an attempt to simulate practical operational rather than ideal conditions and patient outcomes were based solely on the incidence of active trachoma. Among the 314 children who were randomised between the two treatment arms, those receiving azithromycin were significantly more likely to achieve resolution of infection at both 10 weeks (68 vs 51%, $p = 0.007$) and 6 months (88 vs 73%, $p = 0.004$). This was especially evident in those with intense inflammation ($p = 0.023$). Although the differences in efficacy at both follow-up time points were significant in favour of azithromycin, the investigators concluded that as a result of the higher than expected resolution rates associated with topical tetracycline in the absence of supervision, the regular use of the more expensive azithromycin was financially impractical in the absence of medication donation programmes.[25] However, as stated before, this conclusion would have been strengthened through the collection of recurrence rate data as the topical treatment does not address other bodily reservoirs of the pathogen.

In a separate study by Dawson, et al., the efficacy of topical oxytetracycline/polymyxin (once daily for 5 days every 4 weeks for six treatment cycles) was compared with several oral azithromycin regimens (20 mg/kg given either once, once weekly for 3 weeks, or once every 4 weeks for six doses).[11] Although oral placebos were used for the different azithromycin regimens, no placebo was used for the topical treatment arm. The clinical cure rates of the treatments were assessed at 2, 8 and 12 months after the initiation of treatment. Cures were defined primarily by the lack of active trachoma but also secondarily by the presence or absence of inclusion bodies on conjunctival smears. The clinical cure rates were 35% at 2 months, 16% at 8 months and 47% at 12 months. The pretreatment chlamydial infection rate of 33% was decreased to 5% at 2 months and 9% at 12 months. On the basis of the generated data, 1–6 doses of azithromycin produced comparable results to 30 days of topical treatment. However, the authors emphasised the significance of reinfection rates observed at 1 year and the need to evaluate mass-treatment protocols in order to control this endemic disease.

3. Validation of Mass Treatment Strategies

In the process of attempting to eliminate the disease, many studies have investigated recurrence rates in addition to the initial response rates to current treatments.[2,11,12,26-28] The theory behind the

eradication of this infection from endemic areas is based on the lower prevalence of the disease after the administration of antibacterials; therefore, local eradication of the disease can be achieved through repeated, mass treatments.[6,7]

In a study by Laming et al., the impact of target administration of single-dose (20 mg/kg) oral azithromycin to Aboriginal children and their co-resident sibling contacts (ages 6 months to 15 years) was characterised and the results were placed in the context of whole-community treatment strategy (i.e., SAFE) as recommended by the WHO.[27] Acute trachoma prevalence dropped from a baseline of 42% to 22% at 6 months and to 31% at 12 months. Further treatment was given to those who still had trachoma at 12 months, which resulted in a point-prevalence at 24 months of 34%. Prevalence in pre-schoolchildren who were sibling contacts to the infected schoolchildren dropped from a baseline of 55% to 25% at 6 months. The authors concluded from their research that rather than proceeding with mass-treatment strategies, appropriate screening followed by treatment of identified patients leads to a significant decrease in trachoma prevalence in a community. They also recommended that these treatment strategies be combined with appropriate health promotion and attempts to improve living conditions to try to minimise ongoing prevalence not eradicated by treatment.[27]

Because of the substantial rate of reinfection concluded from published trials that evaluated azithromycin,[2,11,29] Fraser-Hurt et al. compared the 2, 6 and 12 month prevalence rates of active trachoma when villagers from eight Gambian villages were mass-treated with either oral azithromycin (weekly for three doses) versus topical tetracycline (daily for 6 weeks).[12] All villagers who were present for the pre-treatment survey were eligible to participate. The villages were matched in pairs of similar size and treatment regimen was allocated randomly within these pairs. At baseline, 16% of the studied villagers were trachoma-positive, defined as the presence of either follicular disease or intense disease as judged by experienced tropical ophthalmologists. Two months after treatment, the prevalence in both groups was approximately 5%. At the 12-month evaluation it was noted that those who had received tetracycline had a prevalence of 16% compared with only 7.7% for those treated with azithromycin. In addition, there were fewer new prevalent cases in the azithromycin group at 12 months and a significantly better rate of trachoma resolution. On the basis of their data, these authors concluded that the convenience of azithromycin may allow for higher coverage than has been previously achieved with standard treatments.

In a study by Schachter et al., pairs of villages in trachoma endemic areas of Egypt, Gambia and Tanzania were matched on trachoma rates in children aged 1–10 years.[28] The matching villages in each area were randomised to receive either 6 weeks of daily topical tetracycline ointment or three weekly doses of azithromycin. Thereafter, the villagers had clinical examinations at approximately 3 and 12 months after their baseline examination and start of treatment. *C. trachomatis* was identified by ligase chain reaction (LCR). Of the study participants who were initially LCR positive, 95% of those who had taken at least one dose of azithromycin were negative at the 3-month follow-up exam compared with 82% of those who received at least 28 days of topical tetracycline. At the 1-year follow-up point, village-wide positivity rates had decreased more substantially in all three geographic areas when the participants received azithromycin compared with tetracycline. Clinical activity was also reduced substantially in those villages that received azithromycin. The authors concluded that the community-wide use of azithromycin markedly reduces infection rates and clinical trachoma in endemic areas, and that it may be an important approach to trachoma control.

Keeping in mind that trachoma is initiated through an infectious process, the use of antibacterials becomes a logical therapeutic step that can also serve to limit the spread of this condition. Currently, the WHO recommends that all children in communities with more than 20% of children pre-

senting with signs and symptoms of active trachoma require antibacterial therapy as part of a mass treatment strategy.[11,12] However, there has been a lot of debate surrounding this issue. On one hand, antibacterials can certainly reduce the number and the overall reservoir pool of ocular chlamydial infections within a community and thus contribute to the decline in transmission rates. However, the persistence of the disease's prevalence as a result of reinfection warrants concern for the eventual development of *C. trachomatis* strains that may carry antibacterial resistant characteristics. Recent data presented by Lietman et al. in 1998 predicts that in regions where trachoma prevalence in children is below 35%, annual or biennial mass treatment would be adequate in eliminating trachoma.[30] However, for areas with prevalence above 35%, biannual mass treatment may be indicated. It is important to note that these estimations assume the universal availability of medication treatments along with no immigration of infected individuals to these villages that have undergone universal treatment.

4. Expert Opinion

On the basis of the clinical studies evaluated, the most widely tested effective treatment strategies for ocular trachoma at this time include topical tetracycline 1% to be applied to both eyes twice daily for 6 weeks or a single oral dose of azithromycin 20mg/kg (up to 1g). Although chemotherapy can generate prompt therapeutic response and surgery can reverse the repercussions of these infections; these conditions will persist through reinfections. Implementing proper personal hygiene and environmental improvement measures for the control of infection transmission will be essential in order to meet the goals of GET2020.[31]

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