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VIEWPOINTS

Development of New Antimicrobials for Urogenital Gonorrhea Therapy: Clinical Trial Design Considerations

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Gonorrhea remains a major public health challenge, and current recommendations for gonorrhea treatment are threatened by evolving antimicrobial resistance and a diminished pipeline for new antibiotics. Evaluations of potential new treatments for gonorrhea currently make limited use of new understanding of the pharmacokinetic and pharmacodynamic contributors to effective therapy, the prevention of antimicrobial resistance, and newer designs for clinical trials. They are hampered by the requirement to utilize combination ceftriaxone/azithromycin therapy as the comparator regimen in noninferiority trials designed to seek an indication for gonorrhea therapy. Evolving gonococcal epidemiology and clinical trial design constraints hinder the enrollment of those populations at the greatest risk for gonorrhea (adolescents, women, and persons infected with antibiotic-resistant *Neisseria gonorrhoeae*). This article summarizes a recent meeting on the evaluation process for antimicrobials for urogenital gonorrhea treatment and encourages the consideration of new designs for the evaluation of gonorrhea therapy.

Keywords. STD clinical trials; gonorrhea treatment; gonococcal antibiotic resistance.

Neisseria gonorrhoeae infections are a global public health problem, occurring disproportionately among persons living on the margins of society, including persons with limited access to health care, limited financial resources, and social and racial minorities. Gonorrhea is a preventable cause of complications and sequelae, which occur disproportionately in women (ie, pelvic inflammatory disease, chronic pelvic pain, infertility, and ectopic pregnancy), and is associated with increased risks for the acquisition and transmission of human immunodeficiency virus. In recent years, the antibiotics most often recommended for gonorrhea treatment have become less effective, in large part related to the inexorable progression of gonococcal antimicrobial resistance [1, 2]. At the same time, antibiotic development has slowed, further hindering efforts to address increasing antimicrobial resistance. The development of new drugs for gonorrhea is time consuming and costly, as are the steps required for the documentation of efficacy needed to obtain regulatory approval for use [2]. For the pharmaceutical industry, when compared to medications that persons may take for prolonged periods or even a lifetime, there is less financial opportunity related to antimicrobial development, particularly for drugs that may be used for single-dose gonorrhea treatments in public health settings. Due in part to these factors, only a single drug, ceftriaxone, currently constitutes the backbone of recommended therapies for gonorrhea treatment worldwide [3, 4]. There are also few easily used, highly effective alternatives to currently recommended therapy for persons who may be allergic to penicillin and other beta-lactam antibiotics or for the treatment of infections due to antibiotic-resistant gonococci.

Designing a trial to evaluate new antimicrobials for gonorrhea treatment is complex. Methods for trial designs, drug pharmacokinetic and drug dosing considerations, statistical determinations of efficacy, optimal study populations, and detection and determinations of study endpoints have all evolved over the past 15–20 years, yet there has been relatively little change in the study designs used for gonorrhea treatment trials. As part of efforts to consider how these and other variables may impact study design and outcomes, in February 2019, experts from a range of disciplines were invited to take part in a discussion of the considerations that might influence clinical trial designs for the evaluation of new antibiotics seeking formal approval for urogenital gonorrhea treatment. Currently, US Food and Drug Administration (FDA) approval of drugs for gonorrhea therapy is based upon treatment efficacy for urogenital infections. Despite emerging data on the prevalence of extragenital (oro-pharyngeal and rectal) gonorrhea, at present urogenital gonorrhea accounts for the majority of direct gonococcal complications (pelvic inflammatory disease in women,

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epididymitis in men, and urogenital abscesses). In this manuscript, we briefly summarize some of these discussions, in the hope of assisting future investigators who are working to make new antimicrobials available for urogenital gonorrhea treatment.

BACKGROUND

The meeting described here was not the first to consider recommendations for trial designs of new antimicrobials for gonorrhea treatment. In 1988, in collaboration with the FDA, the Infectious Diseases Society of America established working groups for the purpose of providing guidelines for the evaluation of new anti-infective drugs, including for sexually transmitted infections. The recommendations of these working groups were published in 1992 and included a recommendation to use a 95% efficacy threshold for new drugs for the treatment of uncomplicated gonorrhea [5]. While not formally adopted as FDA recommendations, this document was powerful and influenced both future clinical trial designs and subsequent considerations of drugs recommended for gonorrhea therapy. Soon thereafter, in a review prepared as background data for revisions of the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Disease (STD) Treatment Guidelines [6], Moran and Levine [7] suggested similar therapeutic standards for gonorrhea; that is, 95% efficacy for ano-genital gonorrhea and 90% for pharyngeal gonococcal infections. In fact, the CDC report also emphasized the desirability of single-dose therapy and recommended even more stringent confidence intervals for the documentation of efficacy for urogenital gonorrhea; that is, >95% efficacy, with a lower bound of the 95% confidence interval of 95% [7]. The impact of these documents continues to be substantial, and they appear to have been informally adopted by the pharmaceutical industry. At the time, newer cephalosporin and fluoroquinolone antibiotics were being regularly studied for gonorrhea; Moran and Levine [7] reported that between 1981 and 1993, there were at least 87 studies of single-dose regimens that evaluated more than 40 drugs for gonorrhea therapy, involved over 24 000 participants, and most commonly evaluated cephalosporin or fluoroquinolone antibiotics. The 1992 Infectious Diseases Society of America recommendations also suggested that, while comparative studies of new drugs were desirable, it seemed possible that in some instances, historical controls might be acceptable [5].

RECENT STUDIES

In recent years, several Phase II and Phase III trials for newer antimicrobials have been carried out. Of the Phase II trials, 2 were dose ranging (zoliflodacin [8] and gepotidacin [9]) and 2 were randomized, controlled trials comparing the new drug to ceftriaxone in doses of 250–500 mg [10, 11]. The Phase II results were promising, with efficacy rates for urogenital infections varying from 96 to 100%, although predictably, due to smaller sample sizes, the confidence intervals for the drugs used uniformly failed to achieve the suggested 90% lower confidence interval [8, 9]. Phase III trials of delafloxacin and solithromycin [10, 11] were also initiated: 1 used ceftriaxone as a comparator and the other used a combination of ceftriaxone and azithromycin, with both trials being stopped prior to completion due to unsatisfactory cure rates. Experience in these trials serves to demonstrate some of the challenges to the assessment of new therapies for gonorrhea treatment.

There is a disconnect between the factors that make gonorrhea a public health priority (eg, complications and sequelae in women, amplification of human immunodeficiency virus risk) and the characteristics of persons who are enrolled in gonorrhea therapy trials. Enrolling participants who are infected with antimicrobial-resistant *N. gonorrhoeae*, women (for whom complications and sequelae are most common), and adolescents (who have the highest infection rates) has proved challenging. This problem arises, in part, related to efforts to reach study endpoints quickly for the purposes of approval or in order to be able to adjust recommendations for therapy in an anticipatory fashion before community treatment failures become unacceptably high. For instance, because resistance has not yet risen to high levels and despite relatively large sample sizes, the proportions of study participants with isolates resistant or less susceptible to current therapy have typically been modest.

In addition, sites where such studies of gonorrhea therapy have most often been conducted, such as STD clinics, most efficiently identify symptomatic males with gonorrhea for enrollment. Barriers to the enrollment of women include: that many gonorrhea infections in women are asymptomatic; that when present, urogenital symptoms in women are nonspecific, hindering the syndromic identification of infected women; and that women at risk for gonorrhea tend to have more options for health care than men, such as in the context of regular reproductive health care. These factors have combined to reduce the numbers of women enrolled in clinical trials of newer therapies for gonorrhea. Yet another recently rediscovered variable that may add to the challenge of recruiting women is that cyclic variations in reproductive hormones may reduce the ability to culture gonorrhea from women during the luteal phase of the menstrual cycle [12]. Further, due to efforts to ensure that unborn children are not exposed to unstudied medications, female study participants may not be pregnant and are required to take measures to not become pregnant during study participation, further constraining their enrollment in drug trials. Similarly, due to appropriate concern regarding the propriety of including children in research, the numbers of the group with the highest rates of sexually transmitted infections—sexually active adolescents—are modest at best. Increasing the numbers of women and adolescents enrolled in trials of newer gonorrhea therapy

increases costs and prolongs the time to completion for the evaluation of new therapies.

PRECLINICAL ANIMAL STUDIES

Bridging *in vitro* susceptibility data to human studies has been challenging due to the lack of suitable animal models for gonorrhea. Over the past decade however, a female mouse model of gonococcal genital tract infection has been increasingly used for preliminary evaluation of candidate antimicrobials for gonorrhea treatment. Jerse and colleagues developed a model using estradiol-treated mice in which the animals can be reliably infected providing an experimentally modifiable means of studying gonococcal virulence factors and different host response variables on gonococcal pathogenesis and the course of experimental infection [13]. The same model has been used to evaluate pharmacokinetic/pharmacodynamic characteristics of antibiotics to guide improved dosing for antibiotics used or suggested for gonorrhea therapy prior to initiation of human trials [14]. Furthermore, the use of hollow fiber models, for example, can also be used to identify optimal dosing regimens prior to initiation of clinical trials, thus ensuring that precious clinical trial resources are used as wisely as possible [15, 16].

PHARMACOLOGIC CONSIDERATIONS

The import of in vitro susceptibility to antibiotics for predicting the risk of treatment failure has been long established. As penicillin became widely used for gonorrhea in the 1950s, investigators documented progressive increases in the minimal inhibitory concentration (MICs) of *N. gonorrhoeae* isolates and began to associate strains with relatively higher MICs with an increased probability of treatment failure [17, 18]. In 1979, Jaffe et al [19] reported on an unpublished study conducted in the 1960s, applying sentinel descriptions of time-dependent microbial killing, which were made in the 1950s by Eagle et al [20], to penicillin therapy for gonorrhea. The study found that penicillin concentrations 3–4 times the MIC for periods exceeding 7–10 hours reliably predicted a cure of gonococcal urethritis. These data were then extended to other antimicrobial classes to become an important contributor to considerations of future drug regimens for gonorrhea treatment.

Recently, improving methods for the evaluation of pharmacokinetic and pharmacodynamic effects on treatment outcomes have become available for a number of other infections, and highlight the pressing need for better data and new research on pharmacokinetic contributors to gonorrhea treatment outcomes [21]. Of the few available studies, in a pharmacokinetic study designed to determine the cefixime dosing required to obtain the drug levels that have been hypothesized as necessary for the reliable treatment of pharyngeal gonorrhea, Barbee et al [22] found that cefixime's absorption kinetics led to plateauing of serum levels despite increasing single doses of the drug, but that a multi-dose regimen met their efficacy target. This suggests that multi-dose regimens may be a method for increasing efficacy. Limited, newer pharmacokinetic data regarding antimicrobial effects, as well as data generated from the murine model of gonococcal infection, have highlighted numerous areas in which additional data are needed. As different antibiotics are considered for gonorrhea therapy, there are numerous gaps among the variables that may impact treatment outcomes. For instance, while beta-lactam antibiotics (penicillins, ceftriaxone, etc.) demonstrate time-dependent bacterial killing, other antibiotics considered for STD treatment, such as fluoroquinolones or azalide antibiotics (eg, azithromycin), exert their antimicrobial effects in a concentration-dependent fashion. Thus, for some drugs, increasing doses may be preferred to improve efficacy, while for other drugs, multiple dose regimens may be preferable to assure prolonged, effective drug levels. Further, antimicrobial activity for different antibiotics may vary according to differential volumes of distribution, differential tissue and fluid concentrations at different sites of potential infection, patient body mass and adiposity, and patient renal function. Finally, host inflammation, which may vary from 1 anatomic site of infection to another, may impact antibiotic concentrations at different mucosal sites of infection (for instance, most gonococcal urethritis in men elicits a substantial inflammatory response, while most pharyngeal and rectal infections are asymptomatic and not accompanied by obvious inflammation). Additional tissue factors, such as pH (which may also be impacted by an inflammatory response) may impact both drug penetration and antimicrobial activity at different sites of infection [23].

It has also become apparent from studies of other infections that the goals of cure and efforts to slow the development of antimicrobial resistance are determined by somewhat different factors [21]. In particular, organism concentrations at the site of infection and bacterial growth rates (which provide more opportunity for mutations to occur) each may impact the likelihood of selection for antimicrobial resistance. Higher bacterial loads often exceed the inverse of the mutational frequency to resistance, raising the probability that there will be a population of less-susceptible organisms present in the total population *a priori*, while more rapid division times favor the development of resistance. A further concern is that drugs with prolonged half-lives, such as azithromycin, will have a prolonged duration of sub-inhibitory antibiotic concentrations, which in turn may tend to select for antibiotic resistance. Thus, the use of azithromycin as part of dual therapy for gonorrhea is unlikely to be slowing the development of antimicrobial resistance, and the rationale for dual therapy with this agent should be reexamined.

MODERN STUDY DESIGN CONSIDERATIONS

For many years, there has been an expectation by clinicians that the recommended, single-dose gonorrhea therapy will reliably

cure infection without the need to adjust treatment based on antimicrobial susceptibility testing or body mass. The preference for this approach reflects confidence derived from the proven reliability of recommended therapies for more than 3 decades, as well the practical need to provide therapy for many patients when clinicians become aware of the likelihood of infection, before test results are available (ie, when persons are diagnosed syndromically, by nonculture methods such as Gram stains, or when persons are identified as sexual partners exposed to persons with gonorrhea), and when there is a concern that patients may not follow up for care. These characteristics, in turn, further complicate the evaluation of new drugs for gonorrhea therapy. Currently, most studies of new drugs for uncomplicated urogenital gonorrhea treatment have been conducted as randomized, noninferiority (as opposed to superiority) trials, most recently using ceftriaxone (with or without azithromycin co-therapy) as the comparator. Because ceftriaxone remains highly effective for gonorrhea treatment, such designs tend to require large sample sizes, particularly if the study goal is to demonstrate that the new drug is not 10% worse than ceftriaxone.

Methods to increase clinical trial efficiency and increase the throughput of products under evaluation are needed. Even with a highly efficacious therapy, such as ceftriaxone, the characteristics of therapeutic alternatives other than urogenital efficacy may be important practical considerations in selecting a preferred therapy. Such characteristics may include therapeutic efficacy at extragenital sites of infection, the frequency of drug allergies and adverse medication effects, routes and convenience of administration, and cost. The desirability of outcome ranking (DOOR) is an approach that synthesizes multiple characteristics providing a global assessment of the comparative value of interventions [24, 25].

An example of an alternate study design is the MASTER protocol for Multiple Infection Diagnostics (MASTERMIND), a study design developed by the Antibacterial Resistance Leadership Group that allows simultaneous evaluation of multiple diagnostic tests in a single study, thereby providing efficiencies through use of a common reference standard, a common protocol, and by evaluating multiple samples from the same study participant [26]. This approach has been applied for studies of *Neisseria gonorrhoeae* diagnostic tests. A MASTERMIND analogue could be applied for urogenital gonorrhea treatment trials to provide an efficient way to simultaneously investigate multiple therapeutic agents in a single trial using a single control group, a common protocol, and standardized definitions and processes. Different experimental arms could be stopped upon demonstration of futility or efficacy, and new arms added after trial initiation with between arm comparisons restricted to use of concurrent data to retain randomization integrity.

To date studies of new drugs carried out in pursuit of FDA approval have used contemporarily approved drugs as comparators. Recent single armed studies such as the evaluations of gemifloxacin or gentamicin, each combined with azithromycin for "salvage therapy" successfully used historical controls and a noncomparative design. To date however, such approaches have not been applied to evaluation of new antimicrobials for FDA approval [27].

For other diseases such as cancer, experts have begun to consider alternative study designs such as instances in which phase II randomized trials, rather than being analyzed as discrete, separate trials, blend into Phase III trials based on the demonstrated efficacy of therapy at a prespecified endpoint. Such designs allow studies of promising interventions to be carried out in a more timely fashion without the logistical challenges of stopping and starting trial enrollment. In some situations, historical controls could also serve to allow efficacy assessment rather than requiring large comparator groups for efficacy demonstration, although such trials may still benefit from smaller groups evaluated for comparative safety and tolerability data.

A combination of newer approaches—for example, implementing desirability of outcome ranking with a noninferiority question—may yield valuable insights into variance among individuals within a population, and the implications of that factor on treatment outcomes, even if the therapy being investigated is not found to be >95% effective.

CLINICAL TRIAL COMPARATOR DRUGS

Since 1985, co-therapy for gonorrhea with a combination of a penicillin and tetracycline was recommended for gonorrhea to address the proven morbidity associated with coexistent *Chlamydia trachomatis* infections [28]. In 1989, to address increasing penicillin resistance, ceftriaxone became the recommended therapy for gonorrhea treatment. At that time, in addition to acknowledging the importance of co-therapy to address the proven risk of chlamydial complications, the CDC Treatment Guidelines first hypothesized that simultaneous treatment with ceftriaxone and a tetracycline might reduce the possibility of treatment failure due to antimicrobial resistance [29]. Since that time, while recommended doses vary, ceftriaxone, administered with antichlamydial co-therapy, has globally remained the preferred and recommended gonorrhea treatment.

Recent US noninferiority gonorrhea treatment trials have used the current standard of care (CDC-recommended treatment)—a single 250 mg injection of ceftriaxone administered with oral azithromycin at 1.0 gram—as the comparator. The use of dual antibiotic comparator arms presents several potential problem for research studies, however. While it has been hypothesized that co-therapy might reduce the rate at which gonococcal antimicrobial resistance progressed, as well as provide coverage for chlamydial coinfections [2, 3], this effect has not been demonstrated when *N. gonorrhoeae* susceptibility

has been monitored over time [29]. In fact, the observation of rapidly developing decreased susceptibility to fluoroquinolone antibiotics despite the widespread administration of antichlamydial co-therapy (typically with azithromycin) seems to argue against this hypothesis, as does declining azithromycin and cephalosporin susceptibility in recent years. Further, the use of combination comparator therapy makes an assessment of the individual drugs used in combination challenging, posing the threat that the efficacy of 1 or both components may erode over time without detection. As an alternative, while the principle of combination therapy to cover coinfecting pathogens is logical for national or global treatment recommendations, some experts suggest that for clinical trials, a head-to-head comparison of the individual components is preferable.

CONCLUSION

New drugs provide a means for addressing what appears to be the inexorable, progressive development of decreasing susceptibility to the drugs used for empiric (ie, without susceptibility testing) treatment of this common threat to personal and public health. The current global reliance (CDC, World Health Organization, European, and UK guidelines) upon a single class of antibiotics (cephalosporins, with ceftriaxone as the archetype) poses a major public health vulnerability to sexual and reproductive health. At the present time, reliance upon ceftriaxone also presents a challenge to clinicians for the management of the large proportion of the population who believe themselves allergic to beta-lactam antibiotics, and the many situations in which an oral alternative to ceftriaxone is needed. Additional drugs or changes to the treatment regimens for gonorrhea therapy are urgently needed. Measures such as the development of gonorrhea tests that simultaneously predict antimicrobial susceptibility (or resistance) to selected antibiotics may serve as temporizing measures, but do not address the remarkable ability of *N. gonorrhoeae* to rapidly develop antibiotic resistance to the drugs used for treatment. To address this problem, there is a need for investigators and the sponsors to consider faster and more efficient means for evaluating new therapies for gonorrhea. To accomplish this will require an effective partnership between the regulatory agencies, who profoundly influence the design of clinical trials aimed at approval of newer antibiotics; the organizations that establish treatment guidelines; industry and collaborating sponsors, who determine the pipeline for the development of new antibiotics; and investigators conducting clinical trials to evaluate new drugs or evolving therapeutic regimens.

Notes

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