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Linezolid in multidrug-resistant tuberculosis

Bolhuis, Mathieu

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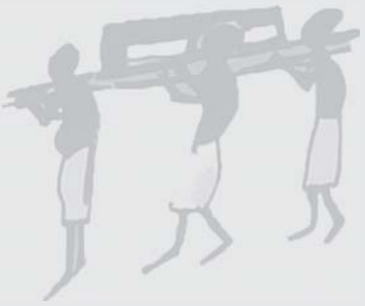

Chapter 7

General discussion and future perspectives

In this thesis, we aimed to describe the clinical pharmacology of linezolid, with special focus on therapeutic drug monitoring (TDM) to optimize treatment of patients suffering from multidrug-resistant tuberculosis (MDR-TB). In order to attain our objectives, we studied the two main areas of pharmacology, *i.e.* the pharmacokinetics (PK) and pharmacodynamics (PD) of linezolid in MDR-TB.

Pharmacokinetic drug-drug interactions

In Chapter 2, we performed a review of literature on drug-drug interactions of linezolid and other drugs from the oxazolidinone group. The multitude of PK drug-drug interactions that are presented in the review of literature (chapter 2) underline that drug-interactions are an important factor to take into account when designing a treatment regimen. In these PK drug-drug interactions, the *perpetrator* changes PK parameters of the *victim*, possibly resulting in a clinically relevant increased or decreased exposure of the *victim* drug. Examples include the interaction between the *perpetrator* clarithromycin and the *victim* linezolid – studied in this thesis – resulting in a significant increase of linezolid exposure (1, 2). This interaction could potentially lead to an increased exposure of linezolid, a drug that is already infamous for its toxicity, forcing clinicians to temporarily cease treatment with linezolid. However, there are also examples of *victim* anti-TB drugs with a decreased exposure as a result of a PK drug-drug interaction. Lowered exposure to subtherapeutic levels could result in acquired resistance, limiting the number of effective drugs even further. Subtherapeutic exposure could also lead to treatment failure – possibly even resulting in death.

From the point of view of tuberculosis treatment, PK drug-drug interactions with the anti-TB drug as a *victim* might be perceived as being of most interest. However, drug interactions with anti-TB drugs as a *perpetrator* are potentially just as important. Suboptimal treatment of co-morbidities might delay or render adequate tuberculosis treatment impossible. Since delay of treatment does not only worsen outcomes of treatment of the individual patient, but also has a negative impact on transmission within a community (3), delay in the initiation of the intensive phase of treatment due to drug-drug interactions might also be unfavourable.

Besides PK drug-drug interactions that are mentioned in summaries of product characteristics (SmPCs) or are known from literature, physicians must always be vigilant for new drug-interactions. For instance, the PK drug-drug interaction between linezolid and clarithromycin (2) is not yet described in the SmPC of linezolid (4). Moreover, the product

information explicitly states linezolid is not metabolised by humane CYP-isoforms (4). This underlines the importance of pharmacovigilance during the post-marketing phase. This is particularly important for drugs that are often used for the treatment of MDR-TB. These anti-MDR-TB drugs are used off-label, such as linezolid and clarithromycin, or on-label but with an accelerated registration program followed by a confirmatory trial, such as bedaquiline (5). Perhaps, an intensive monitoring programme of new anti-TB drugs and new combinations could help to facilitate the gathering of real world clinical data.

Designing treatment regimens

Clinicians often face a difficult challenge when designing treatment regimens consisting of at least four likely effective drugs for the treatment of MDR-TB, as recommended by the World Health Organisation guideline (6). In some low-resources countries, the challenge might be even greater due to lack of available drug susceptibility testing (DST) (7). In these cases, population-based data on DST and surveillance data determine the selection of likely effective drugs to design treatment regimens. However, besides drug susceptibility, there are other factors to take into account when designing a treatment regimen such as pattern of adverse events, drug-drug interactions, route of administration (*e.g.* intravenously versus orally), availability of the drug in the treatment setting, and even costs.

Of these items that should be taken into account when designing a treatment regimen, adverse events deserve special attention. In cases where *in vitro* DST reveals sensitivity, the susceptible drug might not be suitable to add to treatment regimens due to adverse events that have occurred. Most clinical studies on diagnosis or treatment of tuberculosis present data on the *in vitro* drug susceptibility of the included patients. However, the number of feasible treatment options left might even be of greater relevance for clinicians than the number of resistant drugs. In order to allow comparison between clinical studies, it would be helpful to standardize the range of anti-tuberculosis drugs for which DST is performed together with the methods used. A recent study underlined the importance of DST. Perhaps, an addendum on the 2005 manuscript of Laserson *et al.* "Speaking the same language: treatment outcome definitions for MDR-TB" could help to propagate speaking the same language on the subject of DST as well (8).

Targets for Therapeutic Drug Monitoring

Although PK / PD parameters are critically important, unfortunately, there are no clear PK / PD targets yet that can be used for TDM for linezolid. However, several steps were made in defining these targets. For instance, *in vitro* studies revealed maximum killing rates at concentrations twice the MIC (9, 10). Linezolid also showed excellent activity at an AUC (area under the time concentration curve) / MPC_{90} (mutant prevention concentration of 90% of the strains) ratio of 116 in isolates of drug-resistant *M. tuberculosis* (11). At the moment, a linezolid AUC / MIC ratio of at least 100 is strived for in MDR-TB. However, it should be noted that this target ratio is not based on *in vitro* analysis of *M. tuberculosis* isolates but on other microorganisms, such as *Streptococcus pneumoniae* and *Streptococcus aureus* (12). Although there are several arguments suggesting the PK/PD target of an AUC/MIC ratio of 100 might be correct, an *in vitro* PD study is warranted, followed by a clinical validation in a prospective study.

In our retrospective study, in which almost all patients had an AUC/MIC ratio >100, we found no correlation between AUC/MIC ratio and sputum or culture conversion. This might suggest the AUC/MIC ratios were above target at a plateau on which further increasing the ratio does not have a clear effect on efficacy. Perhaps, doses could be lowered even further without loss of efficacy, whilst reducing toxicity.

Obviously, designing clinical PD studies by simply withholding treatment in one cohort is not ethically justified. Unfortunately, PD studies in animals are often not possible due to toxicity in animals at drug exposures that are relevant in humans (13). Because of these limitations, hollow fiber PD infection models of tuberculosis might provide a solution (13). These models take half-lives of drugs and clinically applied dosing schedules into account, mimicking *in vitro* exposure of *M. tuberculosis* in patients to anti-TB drugs as closely as possible. Previously, this method was used to determine the rifampicin PK/PD target in tuberculosis strains, *i.e.* a daily AUC_{0-24h}/MIC of 24 (14). We propose to conduct a similar study to determine an appropriate PK/PD target for linezolid in MDR-TB strains. Once the PK/PD target is more clearly established for linezolid in MDR-TB, the target should be clinically validated.

The identification of the linezolid AUC/MIC ratio for treatment of MDR-TB will possibly reveal a plethora of subjects to study, but more importantly it might improve MDR-TB treatment regimens containing an effective anti-tuberculosis drug. One of the positive effects on the research of the applicability of linezolid in the treatment of MDR-TB could be that

the identification of the linezolid PK/PD target might result in a more homogeneous dosing of linezolid in clinical studies. Results from different studies will be more easily comparable since the attained targets will be similar. This could rapidly increase the number of eligible patients in cohorts of whom TDM data are available, thereby revealing information that would had not have been discovered with small numbers of patients or when too high dosages are applied, a practice that is probably common today (chapter 5).

TDM using standard or alternative sampling techniques, such as DBS sampling or oral fluid sampling, could contribute to limiting adverse effects by tapering the linezolid dose to the lowest possible effective dose. This tapered linezolid dose could particularly be helpful in optimizing treatment regimens of extra vulnerable groups of patients, such a patients with multi-morbidity, pediatric, geriatric, and pregnant or lactating patients. In these patients, pharmacokinetics might be altered. Furthermore, these groups are often not included in studies because of safety reasons, resulting in a lack of and delay on information. Nevertheless, MDR-TB obviously also affects children, the elderly and pregnant women and thus these patients might need to be treated with linezolid as well. In all of the above examples, development of PK models for specific populations is warranted. These PK models for specific patient groups could enable precise dose adjustments based on TDM, resulting in fast attainment of PK/PD targets. These data could also contribute to determining adequate standard dosages for these groups of patients.

As for adding linezolid to treatment regimens of pregnant or lactating patients with MDR-TB, the lack of knowledge on *in utero* effects of linezolid on the pregnant patient and her (unborn) child, the possible efficacy of the drug, the risk of adverse effects and alternatives have to be deliberated by the physician. The fact that untreated MDR-TB is lethal to both the mother and the unborn child and the fact that multidrug-resistance severely limits the number of treatment options that are still feasible, will possibly force clinicians to prescribe linezolid. In these cases, tapering linezolid to the lowest still effective dose could possibly limit the chances of negative effects on the pregnant patients and their (unborn) child. Development of guidelines and increasing the number of peer-reviewed publications on the treatment of pregnant MDR-TB patients including short- and long-term follow-up of the child, would be very helpful for clinicians. This will allow pregnant MDR-TB patients to make better-informed decisions on the risks of treatment.

Linezolid-clarithromycin interaction

Another subject that warrants future study, is the PK drug-drug interaction between linezolid and clarithromycin (chapter 3). After confirming the results in a new cohort, the next step should be to elucidate the underlying mechanism of the interaction. Although several studies refer to an interaction with linezolid as a *victim* and other drugs as a *perpetrator*, as being modified by P-gp (15, 16), this is merely based on one *in vitro* study combined with the summary of product characteristics (4, 17). Both the summary of product characteristics and Wynalda *et al*. state that linezolid is not metabolized through cytochrome P-450 isoenzymes (4, 17). Since the *perpetrator* drugs were P-glycoprotein and cytochrome P-450 3A4 modulators, the hypothesis was postulated that the interaction with linezolid might be P-pg mediated (15, 16). However, there is one article – written by an employee of Pfizer, the manufacturer of linezolid – stating that the linezolid drug-interaction might not be P-gp mediated (18). This raises the question whether Pfizer might have unpublished data on file, contributing to the knowledge on the mechanism of the drug-drug interactions with linezolid as a *victim*. It would be interesting to elucidate the drug-drug interaction, preferably by publishing these data followed by a replication of the study to confirm the findings.

Once the exact mechanism is elucidated, the effect of other *perpetrator* drugs using the same mechanism should be studied. If, for instance, the mechanism turns out to be CYP3A4 mediated, it would be interesting to quantify the effect of other CYP3A4 modulators such as grapefruit juice, carbamazepine or ketoconazole.

Another alluring sequel to the performed prospective PK drug-drug interaction study that we performed would be to quantify the effect of clarithromycin in a higher daily dose than the previously administered 500 mg of clarithromycin, such as a dose of 1000 mg extended release oral formulation once daily. This dose of 1000 mg clarithromycin daily is often administered for several indications without important adverse effects and this dosage is generally well tolerated. The concentration-enhancing effect on linezolid would possibly be more pronounced after administration of 1000 mg clarithromycin than what we observed after administration of 500 mg clarithromycin (2).

The *in vitro* synergy between linezolid and clarithromycin that we described in chapter 6 of this thesis should be followed by studies of other combinations of second line anti-tuberculosis drugs. Investigating *in vitro* synergy could help in optimizing existing treatment regimens. Since the number of anti-TB drugs that emerges from the pipeline

is limited, it is critically important to protect these new drugs from acquiring resistance. Strategies to design and optimize new treatment regimens containing these drugs are warranted.

Elucidating the exact mechanism underlying the observed synergy would contribute to our knowledge of the disease and the mechanism of action of the drugs used. Furthermore, this would possibly answer the question whether the observed synergy is relevant in humans in clinical practice or is only limited to an *in vitro* setting. Detailed knowledge on *synergy*, but also on inhibition, could alter the way treatment regimens are designed.

Generic linezolid: cheap linezolid for everyone?

In May 2015, the patent of linezolid will expire. As a result, cheaper generic versions of linezolid will become available within the following years. As a matter of fact, in India – where the patents of linezolid are not recognized by the authorities – cheaper versions of linezolid have been available for years (19). The lowered price of linezolid will make the drug affordable for a larger group of patients, including patients in low- and middle-income countries. The affordability will possibly lead to an increased incorporation of linezolid in treatment regimens. This, in turn, might result in increased antimycobacterial pressure and the likelihood of emerging resistance increases (20). Clinicians should ensure addition of linezolid to adequate treatment regimens to protect this effective anti-tuberculosis drug. Attention should be paid to adherence, preferably administering linezolid under directly observed therapy (DOT) (21). Therapeutic drug monitoring should be applied to identify subtherapeutic drug exposure of linezolid, but also to identify subtherapeutic exposure of other drugs of the treatment regimen leaving linezolid as monotherapy.

The long treatment duration is one of the great obstacles in treating MDR-TB. The impact on patients of being on treatment for at least 18 months is not to be underestimated. Possibly, the duration of treatment might also be one of the reasons of non-adherence or cessation of treatment. Shortening the treatment duration would have an enormous impact on the treatment of MDR-TB. Shortened treatment duration might not only increase the chances of treatment completion in an adequate manner, but it might also save the tuberculosis programs costs per treated patient. Recently, the shortened 9-months Bangladesh treatment regimen showed promising outcome in over 500 MDR-TB patients (22). In contrast with clofazimin (23) and pretomanid, previously known as PA-284 (24),

there is no clear evidence suggesting linezolid is effective in killing slowly replicating persistent microorganisms (25). However, the effective linezolid might play a future role in a comparable shortened treatment regimen: not as a killer of *persisters* but as an effective anti-MDR-TB drug in the intensive phase. When the saved resources would be used for research in the field of developing new anti-TB drugs, shortening the treatment duration might indirectly even help in reaching the WHO goal of eradicating TB by the year 2050.

However, perhaps in the following years the role of structure analogues of linezolid in treating MDR-TB will become greater than the role of linezolid. Preliminary results in a murine model of one of these analogues, suggest that sutezolid (PNU-100480) may have the potential to shorten TB regimens in both normal sensitive and MDR-TB (26). Another advantage of linezolid structure analogues might be that they display less toxicity than linezolid (10, 27). It will be interesting to study to what extent structure analogues will display less toxicity than linezolid in clinical practice and if findings from this thesis on linezolid, such as the PK drug-drug interaction and *in vitro* synergy with clarithromycin, will also be observed in the newer oxazolidinones.

Conclusion

In the General Introduction of this thesis, we referred to famous African musicians that fell victim to TB. Hopefully, the research in this thesis combined with the studies proposed in the future perspectives part of the General Discussion, will further contribute to the quality of treatment of MDR-TB. Perhaps, the research will contribute to improved treatment in both low- and high-income countries. It might even prevent a modern day African musician from falling victim to TB.

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