Review

Influence of Single Nucleotide Polymorphisms on Rifampin Pharmacokinetics in Tuberculosis Patients

Levin Thomas 1, Sonal Sekhar Miraj 1, Mallayasamy Surulivelrajan 1, Muralidhar Varma 2, Chidananda S. V. Sanju 3 and Mahadev Rao 1,*

1 Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, Karnataka 576104, India; levin.thomas@learner.manipal.edu (L.T.); sonal.sekhar@manipal.edu (S.S.M.); msv.rajan@manipal.edu (M.S.)
2 Department of Infectious Diseases, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka 576104, India; muralidhar.varma@manipal.edu
3 District Tuberculosis Control Office, Ajjarakad, Udupi, Karnataka 576001, India; dtokaudu@rntcp.org
* Correspondence: mahadev.rao@manipal.edu

Received: 6 May 2020; Accepted: 3 June 2020; Published: 8 June 2020

Abstract: Rifampin (RF) is metabolized in the liver into an active metabolite 25-desacetylrifampin and excreted almost equally via biliary and renal routes. Various influx and efflux transporters influence RF disposition during hepatic uptake and biliary excretion. Evidence has also shown that Vitamin D deficiency (VDD) and Vitamin D receptor (VDR) polymorphisms are associated with tuberculosis (TB). Hence, genetic polymorphisms of metabolizing enzymes, drug transporters and/or their transcriptional regulators and VDR and its pathway regulators may affect the pharmacokinetics of RF. In this narrative review, we aim to identify literature that has explored the influence of single nucleotide polymorphisms (SNPs) of genes encoding drug transporters and their transcriptional regulators (SLCO1B1, ABCB1, PXR and CAR), metabolizing enzymes (CES1, CES2 and AADAC) and VDR and its pathway regulators (VDR, CYP27B1 and CYP24A1) on plasma RF concentrations in TB patients on antitubercular therapy. Available reports to date have shown that there is a lack of any association of ABCB1, PXR, CAR, CES1 and AADAC genetic variants with plasma concentrations of RF. Further evidence is required from a more comprehensive exploration of the association of SLCO1B1, CES2 and Vitamin D pathway gene variants with RF pharmacokinetics in distinct ethnic groups and a larger population to reach conclusive information.

Keywords: tuberculosis; rifampin; single nucleotide polymorphisms; SLCO1B1; pharmacokinetics

1. Introduction

Rifampin (RF) was introduced as a part of the combinational chemotherapy regimen for tuberculosis (TB) during the 1960s. This has revolutionized TB treatment by reducing the duration of antitubercular therapy (ATT) and improving the cure rates [1,2]. The antimicrobial effect of RF on Mycobacterium tuberculosis and the development of RF resistance is concentration-dependent [3,4]. RF exhibits antmycobacterial action by arresting the DNA-directed RNA synthesis of Mycobacterium tuberculosis through interaction with the β subunit of RNA polymerase (RNAP) [5,6]. The primary mechanism of RF resistance is due to the mutations in the rpoB gene that encode for the β subunit of RNA polymerase. The most common mutations in the rpoB gene are found in the rpoB 531, rpoB 526 and rpoB 516 codons of the RF resistance determining region (RRDR) [7,8]. Recent evidence has shown that higher doses of RF from the currently recommended dosage regimens resulted in better treatment outcomes in TB patients [9,10]. A recent comprehensive meta-analysis reported a wide range of interstudy heterogeneity in RF pharmacokinetic parameter estimates. Many variables such as
HIV, TB and diabetes status, drug combinations, duration of therapy and dosing frequency could not explain the heterogeneity in the pharmacokinetics of RF. An increase in RF dose from the common weight-based dosing category of 8–12 mg/kg to at least 25 mg/kg was required to achieve plasma pharmacokinetic-pharmacodynamic (PK/PD) targets [11]. Single nucleotide polymorphisms (SNPs) represent the most common type of genetic polymorphism in humans [12]. Multiple studies have reported the association of various genetic polymorphisms with significant variances in plasma RF levels in TB patients. This provides us with an exciting opportunity to review for assessing the potential impact of SNPs as an important driver for plasma RF exposure variability in TB patients.

RF is metabolized in the liver into an active metabolite 25-desacetylrifampin and excreted almost equally via biliary and renal routes [13]. B-esterase and Arylacetamide deacetylase (AADAC) enzymes have been reported to catalyze the deacetylation of RF to 25-deacetylrifampin [14,15]. Membrane drug transporters are recognized to be important determinants of absorption, distribution, metabolism and excretion (ADME) of drugs and consequently influence their pharmacokinetic (PK), therapeutic efficacy and safety profiles. Solute carrier (SLC) transporters and the adenosine triphosphate (ATP)-binding cassette (ABC) transporters represent two superfamilies of membrane drug transporters. They are primarily involved in the in and out transport of drugs across tissues and cells in the human body. The SLC and ABC superfamily account for about 400 membrane transporters, out of which around 32 are clinically relevant [16,17]. Pregnane X receptor (PXR) and constitutive androstane receptor (CAR) are nuclear hormone receptors that are involved in the transcriptional regulation of various drug-metabolizing enzymes and transporters [18]. Multiple studies have revealed the potential role of PXR and CAR in the transcriptional regulation of SLC and ABC proteins [19–21]. RF disposition is influenced by sinusoidal influx transporter SLCO1B1 and efflux transporter ABCB1 during hepatic uptake and biliary excretion, respectively [22–24].

Vitamin D regulates gene transcription by binding to Vitamin D Receptor (VDR). The 427 amino acid VDR is encoded by the VDR gene [25]. Vitamin D is involved in the modulation of innate and adaptive immune responses through the mediation of multiple genes. These genes regulated by the transcription factor VDR encode for proteins that relate to acute response to infection, general functions in infection and for autoimmune responses [26]. The degree of immune responses elicited is associated with the circulating levels of Vitamin D [27]. Vitamin D deficiency (VDD) and VDR gene polymorphisms are associated with an increased risk for the development of TB [28]. VDR has been reported to induce the expression of SLCO1B1 [29]. Furthermore, RF can also result in the reduction of Vitamin D levels by increasing its clearance through the agonist and inducing action on PXR and CYP3A4, respectively [30,31]. Hence, the genetic polymorphisms of these metabolizing enzymes, drug transporters and/or their transcriptional regulators and VDR gene and its pathway regulators may influence the RF pharmacokinetics.

Relevant studies were searched in databases like PubMed, MEDLINE, EMBASE, Web of Science and Google Scholar. The following Medical Subject Headings (MeSH) words were used as part of our search strategy: antitubercular agents, antitubercular drugs, rifampin, rifampicin, genetic polymorphism, genetic susceptibility, pharmacogenetics, pharmacogenomics, genetic association study, genetic association analysis, tuberculosis, single nucleotide polymorphisms, pharmacokinetics, population pharmacokinetics, SLCO1B1, ABCB1, PXR, CAR, carboxylesterase 1 (CES1), carboxylesterase 2 (CES2), AADAC and VDR. The scope of the review is limited to studies that recruited TB patients, regardless of age and HIV status who were either already established on ATT or commencing treatment. Association between at least one genetic variant and RF pharmacokinetic outcome was assessed (Figure 1). Studies without any formal evaluation of genotype effects for RF exposures were excluded. From the reference lists of the articles, we extracted additional literature relevant to the topic. Only publications in the English language were considered for this review.
2. *SLCO1B1*

The organic anion transporting polypeptide 1B1 (OATP1B1) is a 691 amino acid protein expressed predominantly on the basolateral (sinusoidal) membrane of hepatocytes. It is encoded by the solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene (spans 15 exons) located on chromosome 12. OATP1B1 is one of the major membrane influx transporters that regulate the active hepatic uptake of substrates from the bloodstream into the hepatocyte [16,32]. RF is a strong substrate of the OATP1B1 transporter protein [33,34]. Around 190 genomic variants with minor allele frequency higher than 5% were identified with the *SLCO1B1* gene. Among these variants, rs4149056 and rs2306283 have been commonly identified and well-characterized [35].

The missense SNP rs4149056 located in exon 5 (also known as c.521T>C; with T allele defined as the wild-type allele and the C allele as a variant) causes a change of amino acid from valine to alanine at residue 174. This variant is reported to have reduced expression and activity of *SLCO1B1* in vitro and in vivo. Hence, drugs that are substrates for OATP1B1 with c.521T>C may tend to have elevated plasma concentrations due to reduced uptake/transporter activity [36,37]. Allegra et al. have reported higher plasma RF concentrations in TB patients with *SLCO1B1* rs4149056 polymorphism. Multivariate linear regression analysis revealed that *SLCO1B1* rs4149056 genotype was found to be a positive predictive factor for increased plasma RF trough concentration (C$_{\text{trough}}$, $\beta = 0.048$, 95% CI [6.458–1313.556]) and maximum concentration (C$_{\text{max}}$, $p = 0.019$, $\beta = 0.432$, 95% CI [452.896–4571.730]) at second week of ATT [38]. The frequency of *SLCO1B1* rs4149056 genotype was reported to be 28.3%, 5.7%, 14.9% and 14.8% in Amerindian, African descent, Mulatto and Caucasian descent ethnic groups, respectively [39]. Mwinyi et al. reported a frequency of 15% and 12.2% in German and Turkish populations, respectively, whereas 15% prevalence was reported among the UK population for *SLCO1B1* rs4149056 genotype [40,41].

rs2306283 (c.388A>G) is a missense SNP located in the exon 4 of the *SLCO1B1* gene that causes a change of amino acid from asparagine to aspartic acid at amino acid position 130. The functional consequences of this variant reported by different in vitro and in vivo studies have yielded conflicting results and may be substrate-specific [36,42]. Dompreh et al. had reported that the *SLCO1B1* rs2306283 polymorphism was associated with lower RF concentration in the pediatric TB population. Two patients (1.8%) with the *SLCO1B1* *1b* homozygous variant (AA genotype) had significantly lower RF C$_{\text{max}}$ (1.81 (0.81–2.80) µg/mL) and area under the time-concentration curve from 0 to 8 h (9.33 (2.35–16.31) µg*h/mL) and higher apparent oral clearance (44.54 (15.38–73.69) L/h) and apparent volume of distribution.

**Figure 1.** Schematic diagram representing. (1) The genes whose SNPs were assessed with plasma RF concentrations in the review and (2) RF biotransformation.
(109.23 (54.86–163.59) L) than did those with the wild type (GG genotype) in a pairwise analysis [43]. However, other studies have reported higher frequencies of the \textit{SLCO1B1} *1b homozygous variant (AA genotype) in Chilean (18.6%), Macedonian (33.1%) and Albanian (30.8%) population [44,45].

Chigutsa et al. and Gengiah et al. reported a high prevalence of \textit{SLCO1B1} rs4149032 (g.38664C>T), which is an intron 2 haplotype tagging SNP (tSNP). \textit{SLCO1B1} rs4149032 polymorphism was found to be associated with lower RF exposures in the African population suggesting the need for increasing the RF dose [46,47]. The functional consequences of \textit{SLCO1B1} rs4149032 on gene expression and on transporter activity are not yet known. Chigutsa et al. reported an allele frequency of 70% for the \textit{SLCO1B1} rs4149032 polymorphism in the South African pulmonary TB (PTB) patients. Patients who were heterozygous and homozygous for the rs4149032 polymorphism in this population had reductions in RF bioavailability by 18% and 28%, respectively. Simulations showed that \textit{SLCO1B1} rs41490932 carriers had a predicted reduction in C\textsubscript{max} of < 8 mg/L and an increase in the daily rifampin dose by 150 mg in the PTB patients in these population would help in achieving plasma concentrations similar to those of wild-type individuals [46]. Gengiah et al. reported an allele frequency of 76% for the \textit{SLCO1B1} rs4149032 polymorphism in the TB-HIV coinfected patients in South Africa. The median (IQR) RF concentrations at 2.5 h postdose were 3.4 (2.7–4.7) µg/mL, 3.7 (2.8–5.0) µg/mL and 5.3 (3.8–6.7) µg/mL for homozygous variant, heterozygous variant and wild type carriers of \textit{SLCO1B1} rs4149032 polymorphism, respectively, which was well below the recommended target range of 8 to 24 µg/mL [47].

Mukonzo et al. reported an allelic frequency of 66% for the \textit{SLCO1B1} rs4149032 polymorphism in the Ugandan population [48]. Lower RF exposures were reported with \textit{SLCO1B1} rs11045819 polymorphism in a study conducted by Weiner et al. [49]. \textit{SLCO1B1} rs11045819 (c.463 C>A) polymorphism is a missense variant, present on the exon 4 of the \textit{SLCO1B1} that cause a change of amino acid from proline to threonine at amino acid position 155 [49]. \textit{SLCO1B1} rs11045819 polymorphism was found to reduce the systemic exposure of the substrate for OATP1B1 transporter [50]. Weiner et al. reported the prevalence of \textit{SLCO1B1} rs11045819 polymorphism as 19% (n = 7) in African TB patients, 11% (n = 4) in TB patients of US and Spain and 25% (n = 4) among the healthy US population (controls). Patients with the \textit{SLCO1B1} rs11045819 variant allele (CA) had 42% lower RF exposure (25.6 µg*h/mL), 34% lower peak concentration levels (5 µg/mL) and 63% greater apparent oral clearance (22 L/h) compared to the wild type allele (CC) [49].

However, recent studies from the African population have not found any association with \textit{SLCO1B1} polymorphisms and RF exposures among TB patients [48,51,52]. Similarly, studies conducted by Ramesh et al. and Jeremiah et al. in the Indian and Tanzanian population, respectively, did not report any association of \textit{SLCO1B1} polymorphisms with plasma RF exposures (Table 1) [53,54]. The association of \textit{SLCO1B1} rs4149056, rs2306283, rs4149032 and rs11045819 polymorphisms with RF pharmacokinetics reported in certain studies were not replicated in other studies that can be attributed due to multiple factors such as lower sample population, ethnic variations, variations in the criteria and timings of sample collection, analytical variations and interindividual factors such as variations in body weight and medication adherence. Therefore, additional studies are warranted to characterize the functional consequences of \textit{SLCO1B1} rs4149056, rs2306283, rs4149032 and rs11045819 polymorphism on RF pharmacokinetics in other ethnic groups.
Table 1. Influence of SLCO1B1 genetic variants on plasma RF levels.

| SI No. | Author, Year | Population | SNP ID | Criteria of Sample Collection | Time of Sample Collection | RF Concentration in Plasma |
|--------|--------------|------------|--------|--------------------------------|---------------------------|---------------------------|
| 1      | Mukonzo et al., 2020 [48] | 50 TB patients from Uganda | rs4149056 <br>rs2306283 <br>rs4149032 | After 21 days of ATT initiation | Predose, 1, 2, 4, 6 and 12 h postdose | No change <br>No change <br>No change |
| 2      | Naidoo et al., 2019 [51] | 172 recurrent TB patients in South Africa | rs2306283 <br>rs4149032 <br>rs2306283 <br>rs4149015 | 1 and/or 2 months and at 6 months during ATT | Predose, 2.5, 6 and 24 h postdose | No change <br>No change <br>No change <br>No change |
| 3      | Calcagno et al., 2019 [52] | 221 PTB with HIV patients in Uganda | rs4149032 | At 2nd, 4th and 8th week of ATT | 1, 2 and 4 h postdose | No change |
| 4      | Dompreh et al., 2018 [43] | 113 pediatric TB patients in Ghana | rs2306283 <br>rs4149032 <br>rs4149032 <br>rs2306283 <br>rs4149032 | After 4 weeks of ATT | Plasma C<sub>max</sub> (end of 3 infusions for IV route and 2 h postdose for oral) and C<sub>trough</sub> | Decreased <br>No change <br>No change <br>No change <br>No change |
| 5      | Allegra et al., 2017 [38] | 24 TB patients in Italy | rs4149056 | At 2nd week and 4th week of ATT | No change |
| 6      | Sloan et al., 2017 [55] | 174 adult PTB patients in Malawi | rs11045819 <br>rs4149032 | Day 14 or 21 of ATT | Predose, 2 and 6 h postdose | No change <br>No change |
| 7      | Ramesh et al., 2016 [53] | 256 South Indian adult PTB/EPTB patients | rs11045819 <br>rs4149032 <br>rs4149033 | After a minimum of 2 weeks of ATT | 2 h postdose | No change <br>No change <br>No change |
| 8      | Jeremiah et al., 2014 [54] | PTB patients in Tanzania | rs4149032 | 1st occasion: 7 ± 2 days after ATT 2nd occasion: Around 56 days after ATT | 2, 4 and 6 h postdose | No change |
| 9      | Gengiah et al., 2014 [47] | 57 TB with HIV patients in South Africa | rs4149032 | At 4th, 8th and 12th week of TB treatment | 2.5 h postdose | Decreased |
| 10     | Chigutsa et al., 2011 [46] | 60 PTB patients in South Africa | rs4149032 <br>rs4149032 <br>rs11045819 | At least 1 month after the start of ATT | 4 to 8 samples per patient, randomly collected over a 7 h period | Decreased <br>No change <br>No change |
| 11     | Weiner et al., 2010 [49] | 72 TB Patients (37 from Africa and 35 from the United States and Spain) | rs4149015 <br>rs2306283 <br>rs11045819 <br>rs4149032 <br>rs59502379 | Between the 9th and 40th doses in TB patients | Just before dose and 1, 2, 6, 8 to 10, 11 to 13 and 23 to 25 h after dose | No change <br>Decreased <br>No change <br>No change <br>No change |

3. ABCB1

ABCB1 (or MDR1) gene is located on chromosome 7 and consists of 29 exons in a genomic region spanning 251.3 kb. It is one of many ABC genes that encode for the 1280 amino acid ABCB1 transporter.
protein (P-glycoprotein). P-glycoprotein (Pgp) is a multidomain integral membrane protein that utilizes the energy generated from the ATP hydrolysis to translocate solutes or ions from intracellular to extracellular membranes (efflux pump) in eukaryotes [56–58]. RF is a substrate of the Pgp efflux pump [59]. rs1128503, rs2032582 and rs1045642 are the most commonly found SNPs in the ABCB1 gene [60]. rs1128503 and rs1045642 are synonymous mutations, whereas rs2032582 is a missense mutation [61]. None of the studies were able to infer any association between ABCB1 polymorphisms and RF pharmacokinetics (Table 2). These studies have explored the association of only a limited number of ABCB1 polymorphisms with the RF exposures. There are about 8643 single nucleotide variants (SNV) reported for the ABCB1 gene. The functional consequences of rare ABCB1 variants that may have a significant effect on drug pharmacokinetics have not been largely elucidated [58]. Hence, additional studies with other genetic variants are required to establish the impact of ABCB1 polymorphisms with the RF exposure.

### Table 2. Influence of ABCB1 genetic variants on plasma RF levels.

| Sl No. | Author, Year, Year | Population | SNP ID | Criteria of Sample Collection | Time of Sample Collection | RF Concentration in Plasma |
|--------|-------------------|------------|--------|-------------------------------|---------------------------|---------------------------|
| 1      | Naidoo et al., 2019 [51] | 172 recurrent TB patients in South Africa | rs1027603, rs1128503, rs2032582, rs1045642, rs2235033, rs2235013 | 1 and/or 2 months and at 6 months during ATT | Predose, 2.5, 6 and 24 h postdose | No change |
| 2      | Calcagno et al., 2019 [52] | 221 PTB with HIV patients in Uganda | rs1045642 | At 2nd, 4th and 8th week of ATT | 1, 2 and 4 h postdose | No change |
| 3      | Allegra et al., 2017 [38] | 24 TB patients in Italy | rs1045642 | At 2nd week and 4th week of ATT | Plasma $C_{\text{max}}$ (end of 3 infusions for IV route and 2 h postdose for oral) and $C_{\text{trough}}$ | No change |
| 4      | Chigutsa et al., 2011 [46] | 60 PTB patients in South Africa | rs1045642, rs2032582, rs1128503, rs3842 | At least 1 month after the start of ATT | 4 to 8 samples per patient, randomly collected over a 7 h period | No change |

4. PXR and CAR

PXR and the CAR are members of the group I of the subfamily I of nuclear receptors (NRs) that are involved in regulating the transcription of a wide range of drug-metabolizing enzymes and drug transporters genes [62,63]. RF is a substrate for SLCO1B1 and ABCB1 protein and the transcription of genes encoding these proteins are regulated by the PXR and CAR. Few studies have explored the possibility of association of the SNPs of these genes with the plasma RF levels. The PXR (or NR1I2) gene located on chromosome 3 and consisting of 9 exons encodes for the PXR [64]. rs2472677 and rs1523130 variants are present in the intron 1 and 5'UTR regions of the PXR gene, respectively. These regions represent the transcription factor binding sites of PXR regulatory regions [65,66]. The CAR (or NR1I3) gene located on chromosome 1 and consisting of 9 exons encodes for the CAR [67,68]. The rs2307424 variant is due to a synonymous substitution (c.540 C>T) in the CAR gene [69]. None of these SNPs in PXR and CAR affected RF exposures (Tables 3 and 4).
Table 3. Influence of PXR genetic variants on plasma RF levels.

| Sl No. | Author, Year         | Population            | SNP ID      | Criteria of Sample Collection | Time of Sample Collection | RF Concentration in Plasma |
|--------|----------------------|-----------------------|-------------|--------------------------------|---------------------------|----------------------------|
| 1      | Naidoo et al., 2019 [51] | 172 recurrent TB patients in South Africa | rs2472677 rs1523130 | 1 and/or 2 months and at 6 months during ATT | Predose, 2.5, 6 and 24 h postdose | No change No change |
| 2      | Calcagno et al., 2019 [52] | 221 PTB with HIV patients in Uganda | rs2472677 | At 2nd, 4th and 8th week of ATT | Plasma C<sub>max</sub> (end of 3rd infusion for IV route and 2 h postdose for oral) and C<sub>trough</sub> | No change |
| 3      | Allegra et al., 2017 [38] | 24 TB patients in Italy | rs2472677 | At 2nd week and 4th week of ATT | 4 to 8 samples per patient, randomly collected over a 7 h period | No change |
| 4      | Chigutsa et al., 2011 [46] | 60 PTB patients in South Africa | rs2472677 rs1523130 | At least 1 month after the start of ATT | 4 to 8 samples per patient, randomly collected over a 7 h period | No change |

Table 4. Influence of CAR genetic variants on plasma RF levels.

| Sl No. | Author, Year         | Population            | SNP ID      | Criteria of Sample Collection | Time of Sample Collection | RF Concentration in Plasma |
|--------|----------------------|-----------------------|-------------|--------------------------------|---------------------------|----------------------------|
| 1      | Chigutsa et al., 2011 [46] | 60 PTB patients in South Africa | rs2307424 | At least 1 month after the start of ATT | 4 to 8 samples per patient, randomly collected over a 7 h period | No change |

5. CES1 and CES2

RF is primarily metabolized to 25-desacetylrifampin by B-esterase [70]. B-esterases family comprises CES, acetylcholinesterase and butyrylcholinesterase enzymes [14]. Among these enzymes, CES exhibits broad substrate specificity and is involved in the metabolism of a wide range of endobiotic and xenobiotic compounds by hydrolyzing ester, thioester, amide and carbamate linkages. Human CES1 and human CES2 encoded by CES1 and CES2 gene, respectively, represent the two major isoenzymes of CES that are expressed in the liver [71]. Over the past decade, several CES1 and CES2 functional genetic variants associated with significant variations to various drug therapy responses have been reported. Hence, assessing the genetic polymorphisms of these genes with the pharmacokinetics of the substrate drugs becomes relevant [72]. The CES1 and CES2 genes are located on chromosome 16 and consist of 14 and 12 exons, respectively [73].

Sloan et al. reported that the rs12149368 variant present on the exon 1 (5′UTR) region of the CES1 gene does not affect the plasma RF concentration (Table 5) [55]. Song et al. evaluated 10 SNPs: c.-2548C>T and c.-2263A>G variants in the promoter region, c.269-965A>G, c.474-152T>C, c.615 + 120G>A, c.1612 + 136G>A and c.1613-87G>A variants of the intron regions and c.1872*69A>G, c.1872*302_304delGAA, c.1872*445C>T variants of the 3′UTR regions of the CES2 gene with the RF levels. Increased plasma RF concentrations in TB patients were associated with the CES2 c.-22263A>G (g.738A>G) variant. The allelic frequencies for this variant were reported to be 0.33 in TB patients and 0.31 in controls and plasma RF concentrations were 8.9 ± 2.9 mg/L, 10.5 ± 3.1 mg/L and 13.9 ± 7.4 mg/L in homozygotes carrying major allele, heterozygotes and homozygotes carrying minor allele, respectively. Results of luciferase reporter analysis revealed that the change from A to G in CES2 c.-22263A>G variant was associated with a consistent decrease in luciferase activity, which may result
in decreased RF metabolism and increased plasma RF concentration. [74]. However, Dompreh et al. did not find any changes in the RF exposures with the CES2 rs3759994 variant (Table 5) [43].

### Table 5. Influence of CES1 and CES2 genetic variants on plasma RF levels.

| Sl No. | Author, Year     | Population Description            | SNP ID/ Nucleotide Change | Criteria of Sample Collection | Time of Sample Collection | RF Concentration in Plasma |
|--------|------------------|-----------------------------------|---------------------------|-------------------------------|--------------------------|---------------------------|
| 1      | Sloan et al., 2017 [55] | 174 Adult PTB patients in Malawi | rs12149368                | Day 14 or 21 of ATT           | Predose, 2 and 6 h postdose | No change                 |
| 2      | Dompreh et al., 2018 [43] | 113 Pediatric TB patients in Ghana | rs3759994 | After 4 weeks of ATT | Predose, 1, 2, 4 and 8 h postdose | No change |
| 3      | Song et al., 2013 [74] | 35 TB patients in South Korea | rs1803155 rs61733693 | -                              | 2 h postdose | No change |

6. AADAC

AADAC is an enzyme expressed primarily in the human liver and intestine that causes the hydrolysis of many drugs [75]. Nakajima et al. reported that human AADAC was the enzyme responsible for the deacetylation of RF to 25-deacetylrifampin [15]. The AADAC rs1803155 and rs61733693 variants which are missense mutations did not affect any changes in the plasma RF concentrations (Table 6) [55].

### Table 6. Influence of AADAC genetic variants on plasma RF levels.

| Sl No. | Author, Year | Population Description    | SNPs Investigated | Criteria of Sample Collection | Time of Sample Collection | RF Concentration in Plasma |
|--------|--------------|----------------------------|------------------|-------------------------------|--------------------------|---------------------------|
| 1      | Sloan et al., 2017 [55] | 174 Adult PTB patients in Malawi | rs1803155 rs61733693 | Day 14 or 21 of ATT | Predose, 2 and 6 h postdose | No change |

7. Vitamin D Pathway Gene Polymorphisms

The Caudal-type homeobox protein 2 (Cdx2) gene variant found in the regulatory region, FokI variant in exon 2 and BsmI, TaqI and ApaI variants in the 3’end of the VDR gene were found to be associated with TB [76]. BsmI (rs1544410), FokI (rs10735810), TaqI (rs731236) and ApaI (rs7975232) represent the most commonly occurring SNPs of VDR gene [77]. At the fourth week of ATT, univariate regression analysis revealed that FokI TC/CC genotype had a negative predictor role on the plasma RF Ctrough ($p = 0.694$, $β = -0.085$, 95% CI [-1314.809-891.285]), possibly due to stronger transcription of the RF influx protein [38]. The FokI variant codes for a shorter 424 amino acid VDR protein isoform which shows a comparatively higher transcriptional activity by displaying enhanced interaction with transcription factor IIB [78]. Recently, Shaik et al. reported the frequencies of FokI TT, TC and CC genotypes to be 30.2%, 34.4% and 27.7%, respectively, in the Saudi Arabian population [79]. Reports from the Brazilian population revealed the frequencies of FokI TT, TC and CC genotypes to be
44.6%, 41.4% and 14%, respectively [80]. Calcagno et al. reported that the VDR regulatory region Cdx2 variant was not associated with any significant changes in the plasma RF concentration [52].

CYP27B1 and CYP24A1 are two enzymes that are involved in the biotransformation of Vitamin D and play critical roles in governing the 1α,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃) concentration. CYP27B1 gene encodes for the 1α-hydroxylase enzyme that is involved in the activation of 25-hydroxyvitamin D₃ (25-(OH)D₃) to 1,25-(OH)₂D₃ [81]. CYP24A1 is involved in catalyzing the C-23 and C-24 hydroxylation pathways of 25-OH-D₃ and 1,25-(OH)₂D₃ [82]. Hence, genetic variants of these genes may alter the Vitamin D levels and may thereby render TB susceptibility as well as alter RF concentrations in plasma. Allegra et al. reported that the CYP24A1 rs927650 and CYP27B1 rs4646536 variants increased plasma RF concentrations which may probably be explained by the increased activation of Vitamin D, resulting in reduced RF elimination (Table 7) [38]. Multivariate linear regression analysis revealed that CYP27B1 rs4646536 variant (+ 2838C>T; CC/CT genotype) located at intron 6 was a positive factor for RF Cmax concentration ((p = 0.024, β = 0.416, 95% CI [469.172–5857.279]) at second week of ATT. Univariate linear regression analysis revealed that for the CYP24A1 rs927650 (22776C>T) variant located at intron 11, the homologous mutant profile (TT) is a positive predictor factor of RF Ctrough ((p = 0.924, β = −0.021, 95% CI [-1148.256-1055.303]) at fourth week of ATT [38]. The distribution of CYP27B1 rs4646536 TT, TC and CC genotypes were reported to be 45.7%, 40.4% and 13.9%, respectively, in healthy controls of Germany which were in near similar lines with a previously conducted study among 7435 healthy controls of UK [83,84]. The clear functional status of CYP27B1 rs4646536 is unknown. Intronic variants could influence gene expression by affecting the binding of transcription factors and mRNA splicing [85,86]. Hence, an allele variation of rs4646536 from C to T can cause abnormal expression of CYP27B1, resulting in the alteration of Vitamin D levels. CYP27B1 rs4646536 was associated with Vitamin D levels and Vitamin-D-related diseases [84]. The frequencies of CYP24A1 rs927650 TT, CT and CC genotypes were reported to be 26.1%, 49.7% and 24.2%, respectively, in the healthy controls of Germany and 21.3%, 50.8% and 27.9%, respectively, among type 1 diabetes German patients [83,87]. 1α,25(OH)₂D₃ exhibit genomic actions that are mediated through the ligand-binding to the VDR, which forms a heterodimer with retinoid x receptor alpha (RXRα) and subsequently binds to Vitamin D response elements (VDRE) to either enhance or repress transcription of various genes [88]. The CYP24A1 gene has a significant role in 1,25(OH)₂D₃ signaling as the promoter region of the CYP24A1 gene contains VDRE [89]. Polymorphisms in a VDRE of the CYP24A1 gene could reduce the receptor protein binding, transactivation and expression of the CYP24A1 gene in vivo [90]. A suggestive relationship between the CYP24A1 SNP rs927650 and concentrations of 25(OH)D was reported by Hibler et al. [91]. Further research investigating the influence of CYP27B1 and CYP24A1 variants on Vitamin D levels and consequently on RF exposures are required to establish conclusive evidence.
Table 7. Influence of VDR, CYP24A1 and CYP27B1 genetic variants on plasma RF levels.

| Sl No. | Author, Year | Population | Gene | SNP ID | Pharmacokinetic Sampling | Sample Timing | RF Concentration in Plasma |
|--------|--------------|------------|------|-------|---------------------------|---------------|---------------------------|
| 1      | Calcagno et al., 2019 [52] | 221 PTB with HIV patients in Uganda | VDR | rs11568820 (Cdx2) | At 2nd, 4th and 8th week of ATT | 1, 2 and 4 h postdose | No change |
|        |              |            |      | rs731236 (Taql) | | | No change |
|        |              |            |      | rs10735810 (FokI) | | | No change |
|        |              |            |      | rs1544410 (RsalI) | | | No change |
|        |              |            |      | rs11568820 (Cdx2) | | | No change |
| 2      | Allegra et al., 2017 [38] | 24 TB patients in Italy | VDR | rs7979232 (ApaI) | At 2nd week and 4th week of ATT | Plasma C_{max} (end of 3 infusions for IV route and 2 h postdose for oral) and C_{trough} | Decreased |
|        |              |            |      | rs927650 | | | No change |
|        |              |            |      | rs2248359 | | | No change |
|        |              |            |      | rs2585428 | | | No change |
|        | CYP24A1      | rs464536    |       |       | | | Increased |
|        |              | rs10877012  |       |       | | | No change |
|        | CYP27B1      | rs464536    |       |       | | | Increased |
|        |              | rs10877012  |       |       | | | No change |

8. Conclusions

Pharmacokinetic heterogeneity in RF levels represents an austere and ubiquitous problem in TB patient care. This can lead to therapeutic inefficacy, resistance, adverse drug events and increased healthcare expenditures. Genetic variants of SLCO1B1, ABCB1 and VDR have attracted scientific attention for their influence on the pharmacokinetics of a wide range of drugs. While there is a vast number of studies that have explored the influence of SNPs with Isoniazid levels in plasma, only a limited number of studies have explored the influence of genetic variants on the RF pharmacokinetics. Evidence available to date reported a lack of any association of ABCB1, PXR, CAR, CES1 and AADAC genetic variants with the RF concentrations in plasma. Some literature has shown an association of certain genetic variants of SLCO1B1, CES2 and Vitamin D pathway genes with significant variations of RF concentration in plasma. A comprehensive exploration of the role of genetic variants of these genes can be initiated to provide a consensus agreement on their influence on RF pharmacokinetics in different populations.

Genotyping offers to be a potential tool of precision medicine for predicting individual drug-metabolizing and drug transport capabilities before initiation of RF treatment. Further studies assessing RF exposure and correlating it with the genetic polymorphisms are required in different ethnic populations. Besides, such research should be based on a representative and appropriate sample size to validate and implement a cost-effective genotyping-based RF dosage optimization in clinical settings and national policy levels.

Author Contributions: Conceptualization, L.T. and M.R.; writing—original draft preparation, L.T., and M.R.; writing—review and editing, L.T., S.S.M., M.S., M.V., C.S.V.S. and M.R.; supervision, M.R. All authors have read and agreed to the published version of the manuscript.

Funding: This review received no external funding.

Acknowledgments: L.T. is thankful to TMA Pai PhD Scholarship from Manipal Academy of Higher Education, Manipal.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Murray, J.F.; Schraufnagel, D.E.; Hopewell, P.C. Treatment of tuberculosis. A historical perspective. *Ann. Am. Thorac. Soc.* 2015, 12, 1749–1759. [CrossRef] [PubMed]

2. Maggi, N.; Pasqualucci, C.; Ballotta, R.; Sensi, P. Rifampicin: A new orally active rifamycin. *Chemotherapy* 1966, 11, 285–292. [CrossRef] [PubMed]
3. Gumbo, T.; Louie, A.; DeZiel, M.R.; Liu, W.; Parsons, L.M.; Sallinger, M.; Drusano, G.L. Concentration-dependent mycobacterium tuberculosis killing and prevention of resistance by rifampin. *Antimicrob. Agents Chemother.* 2007, 51, 3781–3788. [CrossRef] [PubMed]

4. Alsultan, A.; Peloquin, C.A. Therapeutic drug monitoring in the treatment of tuberculosis: An update. *Drugs* 2014, 74, 839–854. [CrossRef] [PubMed]

5. McClure, W.R.; Cech, C.L. On the mechanism of rifampicin inhibition of RNA synthesis. *J. Biol. Chem.* 1978, 253, 8949–8956.

6. Rastogi, N.; David, H. Mode of action of antituberculous drugs and mechanisms of drug resistance in Mycobacterium tuberculosis. *Res. Microbiol.* 1993, 144, 133–143. [CrossRef]

7. Nakajima, A.; Fukami, T.; Kobayashi, Y.; Watanabe, A.; Nakajima, M.; Yokoi, T. Human arylacetamide deacetylase is responsible for deacetylation of rifamycins: Rifampicin, rifabutin, and rifapentine. *J. Biol. Chem.* 1993, 268, 8949–8956. [CrossRef] [PubMed]

8. Zaw, M.T.; Emran, N.A.; Lin, Z. Mutations inside rifampicin-resistance determining region of rpoB gene associated with rifampicin-resistance in Mycobacterium tuberculosis. *J. Infect. Public Health* 2018, 11, 605–610. [CrossRef]

9. Seijger, C.; Hofsloot, W.; Guchteneire, I.B.-D.; Brake, L.T.; Van Ingen, J.; Kuipers, S.; Van Crevel, R.; Aarnoutse, R.; Boeree, M.; Magis-Escurra, C.; et al. High-dose rifampicin in tuberculosis: Experiences from a Dutch tuberculosis centre. *PloS ONE* 2019, 14, e0213718. [CrossRef]

10. Svensson, E.M.; Svensson, R.J.; Brake, L.H.M.T.; Boeree, M.J.; Heinrich, N.; Konsten, S.; Churchyard, G.; Dawson, R.; Diacon, A.H.; Kibiki, G.S.; et al. The potential for treatment shortening with higher rifampicin doses: Relating drug exposure to treatment response in patients with pulmonary tuberculosis. *Clin. Infect. Dis.* 2018, 67, 34–41. [CrossRef]

11. Stott, K.; Pertinez, H.; Sturkenboom, M.; Boeree, M.J.; Ramachandran, G.; Requena-Méndez, A.; Peloquin, C.; Koegelenberg, C.E.; et al. Pharmacokinetics of rifampicin in adult TB patients and healthy volunteers: A systematic review and meta-analysis. *J. Antimicrob. Chemother.* 2018, 73, 2305–2313. [CrossRef]

12. Wang, D.G.; Fan, J.B.; Siao, C.J.; Berno, A.; Young, P.; Sapolsky, R.; Ghandour, G.; Perkins, N.; Winchester, E.; Spencer, J.; et al. Large-scale identification, mapping, and genotyping of single-nucleotide polymorphisms in the human genome. *Science* 1998, 280, 1077–1082. [CrossRef]

13. Acocella, G. Clinical pharmacokinetics of rifampicin. *Clin. Pharmacokinet.* 1978, 3, 108–127. [CrossRef]

14. Liederer, B.M.; Borchardt, R.T. Enzymes involved in the bioconversion of ester-based prodrugs. *J. Pharm. Sci.* 2006, 95, 1177–1195. [CrossRef]

15. Nakajima, A.; Fukuami, T.; Kobayashi, Y.; Watanabe, A.; Nakajima, M.; Yokoi, T. Human arylacetamide deacetylase is responsible for deacetylation of rifamycins: Rifampicin, rifabutin, and rifapentine. *Biochem. Pharmacol.* 2011, 82, 1747–1756. [CrossRef] [PubMed]

16. Giacomini, K.M.; Huang, S.M.; Tweedie, D.J.; Benet, L.Z.; Brouwer, K.L.; Chu, X.; Dahlin, A.; Evers, R.; Fischer, V.; Hillgren, K.M.; et al. Membrane transporters in drug development. *Nat. Rev. Drug Discov.* 2010, 9, 215–236. [CrossRef] [PubMed]

17. Hillgren, K.M.; Kepller, D.; A Zur, A.; Giacomini, K.M.; Steiger, B.; Cass, C.E.; Zhang, L. Emerging transporters of clinical importance: An update from the international transporter consortium. *Clin. Pharmacol. Ther.* 2013, 94, 52–63. [CrossRef] [PubMed]

18. Gao, J.; Xie, W. Pregnane X receptor and constitutive androstane receptor at the crossroads of drug metabolism and energy metabolism. *Drug Metab. Dispos.* 2010, 38, 2091–2095. [CrossRef]

19. Hagenbuch, B.; Meier, P.J. Organic anion transporting polypeptides of the OATP/ SLC21 family: Phylogenetic classification as OATP/ SLCO superfamily, new nomenclature and molecular/functional properties. *Pflüger Arch.* 2004, 447, 653–665. [CrossRef]

20. Mills, J.B.; Rose, K.A.; Sadagopan, N.; Sahi, J.; De Morais, S.M.F. Induction of drug metabolism enzymes and MDR1 using a novel human hepatocyte cell line. *J. Pharmaco. Exp. Ther.* 2004, 309, 303–309. [CrossRef]

21. Wang, X.; Sykes, D.B.; Miller, D.S. Constitutive androstane receptor-mediated up-regulation of ATP-driven xenobiotic efflux transporters at the blood-brain barrier. *Mol. Pharmacol.* 2010, 78, 376–383. [CrossRef]

22. Guo, Y.X.; Xu, X.F.; Zhang, Q.Z.; Li, C.; Deng, Y.; Jiang, P.; He, L.Y.; Peng, W.X. The inhibition of hepatic bile acids transporters Ntcp and Bsep is involved in the pathogenesis of isoniazid/rifampicin-induced hepatotoxicity. *Toxicol. Mech. Methods* 2015, 25, 1–6. [CrossRef]
23. Brake, L.H.T.; Russel, F.G.; Heuvel, J.J.V.D.; De Knegt, G.J.; De Steenwinkel, J.; Burger, D.M.; Aarnoutse, R.E.; Koenderink, J.B. Inhibitory potential of tuberculosis drugs on ATP-binding cassette drug transporters. *Tuberculosis* 2016, 96, 150–157. [CrossRef]

24. Shugarts, S.; Benet, L.Z. The role of transporters in the pharmacokinetics of orally administered drugs. *Pharm. Res.* 2009, 26, 2039–2054. [CrossRef] [PubMed]

25. Miyamoto, K.; Kesterson, R.A.; Yamamoto, H.; Taketani, Y.; Nishiwaki, E.; Tsutumi, S.; Inoue, Y.; Morita, K.; Takeda, E.; Pike, J.W.; et al. Structural organization of the human vitamin D receptor chromosomal gene and its promoter. *Mol. Endocrinol.* 1997, 11, 1165–1179. [CrossRef] [PubMed]

26. Koivisto, O.; Hanel, A.; Carlberg, C. Key Vitamin D target genes with functions in the immune system. *Nutrients* 2020, 12, 1140. [CrossRef] [PubMed]

27. Caraba, A.; Crişan, V.; Romenşan, I.; Mozos, I.; Murariu, M.-S. Vitamin D status, disease activity, and endothelial dysfunction in early rheumatoid arthritis patients. *Dis. Markers* 2017, 2017, 1–7. [CrossRef]

28. Gao, L.; Tao, Y.; Zhang, L.; Jin, Q. Vitamin D receptor genetic polymorphisms and tuberculosis: Updated systematic review and meta-analysis. *Int. J. Tuberc. Lung Dis.* 2010, 14, 15–23.

29. Saeki, M.; Kurose, K.; Tohkin, M.; Hasegawa, R. Identification of the functional vitamin D response elements in the human MDR1 gene. *Biochem. Pharmacol.* 2008, 76, 531–542. [CrossRef]

30. Wang, Z.; Lin, Y.S.; Zheng, X.E.; Senn, T.; Hashizume, T.; Scan, M.; Dickmann, L.J.; Nelson, S.D.; Baillie, T.A.; Hebert, M.F.; et al. An inducible cytochrome P450 3A4-dependent vitamin D catabolic pathway. *Mol. Pharmacol.* 2011, 81, 498–509. [CrossRef]

31. Xu, Y.; Hashizume, T.; Shubart, M.C.; Davis, C.L.; Nelson, W.L.; Sakaki, T.; Kalhorn, T.F.; Watkins, P.B.; Schuetz, E.G.; Thummel, K.E.; et al. Intestinal and hepatic CYP3A4 catalyze hydroxylation of 1α,25-dihydroxyvitamin D3: Implications for drug-induced osteomalacia. *Mol. Pharmacol.* 2005, 69, 56–65. [CrossRef] [PubMed]

32. Niemi, M. Role of OATP transporters in the disposition of drugs. *Pharmacogenomics* 2007, 8, 787–802. [CrossRef] [PubMed]

33. Vavricka, S.; Van Montfoort, J.; Ha, H.R.; Meier, P.J.; Fattinger, K. Interactions of rifamycin SV and rifampicin with organic anion uptake systems of human liver. *Hepatology* 2002, 36, 164–172. [CrossRef] [PubMed]

34. Treiber, A.; Schneiter, R.; Häusler, S.; Stieger, B. Bosentan is a substrate of human OATP1B1 and OATP1B3: Inhibition of hepatic uptake as the common mechanism of its interactions with Cyclosporin A, rifampicin, and sildenafil. *Drug Metab. Dispos.* 2007, 35, 1400–1407. [CrossRef] [PubMed]

35. Oshiro, C.; Mangravite, L.M.; Klein, T.; Altman, R. PharmGKB very important pharmacogene: SLCO1B1. *Pharm. Genom.* 2010, 20, 211–216. [CrossRef] [PubMed]

36. Niemi, M.; Pasanen, M.K.; Neuvonen, P.J. Organic anion transporting polypeptide 1B1: A genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacol. Rev.* 2011, 63, 157–181. [CrossRef]

37. Pasanen, M.K.; Backman, J.T.; Neuvonen, P.J.; Niemi, M. Frequencies of single nucleotide polymorphisms and haplotypes of organic anion transporting polypeptide 1B1 SLCO1B1 gene in a Finnish population. *Eur. J. Clin. Pharmacol.* 2006, 62, 409–415. [CrossRef]

38. Allegra, S.; Fatiguso, G.; Calcagno, A.; Baietto, L.; Motta, I.; Favata, F.; Cusato, J.; Bonora, S.; Di Perri, G.; D’Avolio, A.; et al. Role of vitamin D pathway gene polymorphisms on rifampicin plasma and intracellular pharmacokinetics. *Pharmacogenomics* 2017, 18, 865–880. [CrossRef] [PubMed]

39. Santos, P.C.; Soares, R.A.; Nascimento, R.M.; Machado-Coelho, G.L.; Mill, J.G.; Krieger, J.E.; Pereira, A.D.C. SLCO1B1 rs4149056 polymorphism associated with statin-induced myopathy is differentially distributed according to ethnicity in the Brazilian general population: Amerindians as a high risk ethnic group. *BMC Med. Genet.* 2011, 12, 136. [CrossRef] [PubMed]

40. Mwinyi, J.; Köpke, K.; Schaefer, M.; Roots, I.; Gerloff, T. Comparison of SLCO1B1 sequence variability among German, Turkish, and African populations. *Eur. J. Clin. Pharmacol.* 2008, 64, 257–266. [CrossRef] [PubMed]

41. Link, E.; Parish, S.; Armitage, J.; Bowman, L.; Heath, S.; Matsuda, F.; Gut, I.; Lathrop, M.; Collins, R. SLCO1B1 variants and statin-induced myopathy—A genomewide study. *N. Engl. J. Med.* 2008, 359, 789–799. [CrossRef] [PubMed]

42. Lee, H.H.; Ho, R.H. Interindividual and interethnic variability in drug disposition: Polymorphisms in organic anion transporting polypeptide 1B1 (OATP1B1;SLCO1B1). *Br. J. Clin. Pharmacol.* 2017, 83, 1176–1184. [CrossRef]
43. Dompreh, A.; Tang, X.; Zhou, J.; Yang, H.; Topletz, A.; Ahwireng, E.A.; Antwi, S.; Enimil, A.; Langaae, T.; Peloso, C.A.; et al. Effect of genetic variation of NAT2 on isoniazid and SLCO1B1 and CES2 on rifampin pharmacokinetics in Ghanaian children with tuberculosis. *Antimicrob. Agents Chemother.* 2017, 62. [CrossRef]

44. Prado, Y.; Saavedra, N.; Zambrano, T.; Lagos, J.; Rosales, A.; Salazar, L. SLCO1B1 c.388A>G polymorphism is associated with HDL-C levels in response to atorvastatin in Chilean individuals. *Int. J. Mol. Sci.* 2015, 16, 20609–20619. [CrossRef]

45. Grapci, A.D.; Dimovski, A.J.; Kapedanovska, A.; Vavlukis, M.; Eftimov, A.; Matevska-Geshkovska, N.; Labachevski, N.; Jakovkovs, K.; Gorani, D.; Kedev, S.; et al. Frequencies of single-nucleotide polymorphisms and haplotypes of the SLCO1B1 gene in selected populations of the western balkans. *Balk. J. Med. Genet.* 2015, 18, 5–21. [CrossRef]

46. Chigutsa, E.; Visser, M.E.; Swart, E.C.; Denti, P.; Pushpakom, S.; Egan, D.; Holford, N.H.; Smith, P.J.; Maartens, G.; Owen, A.; et al. The SLCO1B1 rs4149032 polymorphism is highly prevalent in South Africans and is associated with reduced rifampin concentrations: Dosing implications. *Antimicrob. Agents Chemother.* 2011, 55, 4122–4127. [CrossRef] [PubMed]

47. Gengiah, T.; Botha, J.H.; Soowamber, D.; Naidoo, K.; Karim, S.S.A. Low rifampicin concentrations in tuberculosis patients with HIV infection. *J. Infect. Dev. Ctries.* 2014, 8, 987–993. [CrossRef]

48. Mukonzo, J.K.; Kengo, A.; Kutesa, B.; Nanzigu, S.; Pohanka, A.; McHugh, T.D.; Zumla, A.; Aklillu, E. Role of pharmacogenetics in rifampicin pharmacokinetics and the potential effect on TB-rifampicin sensitivity among Ugandan patients. *Trans. R. Soc. Trop. Med. Hyg.* 2019, 114, 107–114. [CrossRef] [PubMed]

49. Weiner, M.; Peloso, C.; Burman, W.; Luo, C.-C.; Engle, M.; Prihoda, T.J.; Mac Kenzie, W.R.; Bliven-Sizemore, E.; Johnson, J.L.; Vernon, A. Effects of tuberculosis, race, and human gene SLCO1B1 polymorphisms on rifampin concentrations. *Antimicrob. Agents Chemother.* 2010, 54, 4192–4200. [CrossRef] [PubMed]

50. Dudenkov, T.M.; Ingle, J.N.; Buzdar, A.U.; Robson, M.E.; Kubo, M.; Ibrahim-Zada, I.; Batzler, A.; Jenkins, G.D.; Pietrzak, T.L.; Carlson, E.E.; et al. SLCO1B1 polymorphisms and plasma estrone conjugates in postmenopausal women with ER+ breast cancer: Genome-wide association studies of the estrone pathway. *Breast Cancer Res. Treat.* 2017, 164, 189–199. [CrossRef] [PubMed]

51. Naidoo, A.; Chirehwa, M.T.; Ramsuran, V.; McIleron, H.; Naidoo, K.; Yende-Zuma, N.; Singh, R.; Ngcapu, S.; Adamson, J.; Govender, K.; et al. Effects of genetic variability on rifampicin and isoniazid pharmacokinetics in South African patients with recurrent tuberculosis. *Pharmacogenomics* 2019, 20, 225–240. [CrossRef] [PubMed]

52. Calcagno, A.; Cusato, J.; Sekaggya-Wiltshire, C.; Von Braun, A.; Motta, I.; Turyasingura, G.; Castelnuovo, B.; Fehr, J.; Di Perri, G.; Lamorde, M.; et al. The influence of pharmacogenetic variants in HIV/Tuberculosis coinfected patients in South Africa in the SOUTH study. *Clin. Pharmacol. Ther.* 2019, 106, 450–457. [CrossRef] [PubMed]

53. Ramesh, K.; Kumar, A.K.H.; Kannan, T.; Vijayalakshmi, R.; Sudha, V.; Neskumar, S.M.; Bharathiraja, T.; Lavanya, J.; Swaminathan, S.; Ramachandran, G.; et al. SLCO1B1 gene polymorphisms do not influence plasma rifampicin concentrations in a South Indian population. *Int. J. Tuberc. Lung Dis.* 2016, 20, 1231–1235. [CrossRef] [PubMed]

54. Jeremiah, K.; Denti, P.; Chigutsa, E.; Faurelh-Jepsen, D.; PrayGod, G.; Range, N.; Castel, S.; Wiesner, L.; Hagen, C.M.; Christiansen, M.; et al. Nutritional supplementation increases rifampin exposure among tuberculosis patients coinfected with HIV. *Antimicrob. Agents Chemother.* 2014, 58, 3468–3474. [CrossRef]

55. Sloan, D.; McCallum, A.D.; Schipani, A.; Egan, D.; Mwandumba, H.C.; Ward, S.; Waterhouse, D.; Banda, G.; Allain, T.J.; Owen, A.; et al. Genetic determinants of the pharmacokinetic variability of rifampin in malawian adults with pulmonary tuberculosis. *Antimicrob. Agents Chemother.* 2017, 61, e00210-17. [CrossRef] [PubMed]

56. Jones, P.M.; George, A.M. The ABC transporter structure and mechanism: Perspectives on recent research. *Cell. Mol. Life Sci.* 2004, 61, 682–699. [CrossRef]

57. Gottesman, M.M.; Hrycyna, C.; Schoenlein, P.V.; Germann, U.; Pastan, I. Genetic analysis of the multidrug transporter. *Annu. Rev. Genet.* 1995, 29, 607–649. [CrossRef]

58. Wolking, S.; Schaeffeler, E.; Lerche, H.; Schwab, M.; Nies, A.T. Impact of genetic polymorphisms of ABCB1 (MDR1, P-Glycoprotein) on drug disposition and potential clinical implications: Update of the literature. *Clin. Pharmacokinet.* 2015, 54, 709–735. [CrossRef]
59. Schuetz, E.G.; Schinkel, A.H.; Relling, M.V.; Schuetz, J.D. P-glycoprotein: A major determinant of rifampin-inducible expression of cytochrome P4503A in mice and humans. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 4001–4005. [CrossRef]

60. Hodges, L.M.; Markova, S.M.; Chinn, L.W.; Gow, J.M.; Kroetz, D.L.; Klein, T.E.; Altman, R.B. Very important pharmacogene summary: ABCB1 (MDR1, P-glycoprotein). *Pharm. Genom.* **2011**, *21*, 152–161. [CrossRef]

61. Fung, K.L.; Gottesman, M.M. A synonymous polymorphism in a common MDR1 (ABCB1) haplotype shapes protein function. *Biochim. Biophys. Acta* **2009**, *1794*, 860–871. [CrossRef]

62. Moore, D.D.; Kato, S.; Xie, W.; Mangelsdorf, D.J.; Schmidt, D.R.; Xiao, R.; Kliwer, S.A. International union of pharmacology. LXII. The NR1H and NR1I receptors: Constitutive androstane receptor, pregnane X receptor, farnesoid X receptor α, farnesoid X receptor β, liver X receptor α, liver X receptor β, and vitamin D receptor. *Pharmacol. Rev.* **2006**, *58*, 742–759. [CrossRef] [PubMed]

63. Chen, Y.; Tang, Y.; Guo, C.; Wang, J.; Boral, D.; Nie, D. Nuclear receptors in the multidrug resistance through their role in the regulation of drug-metabolizing enzymes and drug transporters. *Biochem. Pharmacol.* **2012**, *83*, 1112–1126. [CrossRef] [PubMed]

64. Lamba, J.; Lamba, V.; Strom, S.; Venkataramanan, R.; Schuetz, E. Novel single nucleotide polymorphisms in the promoter and intron 1 of human pregnane X receptor/NR1I2 and their association with CYP3A4 expression. *Drug Metab. Dispos.* **2007**, *36*, 169–181. [CrossRef] [PubMed]

65. Moore, D.R.; Jorge, A.A.L.; Mendonca, B.B.; Bachega, T.A. Frequency of genetic polymorphisms of PXR gene in the Brazilian population. *Clinics (Sao Paulo)* **2011**, *66*, 1041–1044. [CrossRef] [PubMed]

66. Auerbach, S.S. Alternatively spliced isoforms of the human constitutive androstane receptor. *Nucleic Acids Res.* **2003**, *31*, 3194–3207. [CrossRef]

67. Swart, M.; Whitehorn, H.; Ren, Y.; Smith, P.J.; Ramesar, R.; Dandara, C. PXR and CAR single nucleotide polymorphisms influence plasma efavirenz levels in South African HIV/AIDS patients. *BMC Med. Genet.* **2012**, *13*, 112. [CrossRef]

68. Jinno, H.; Tanaka-Kagawa, T.; Hanioka, N.; Ishida, S.; Saeki, M.; Soyama, A.; Itoda, M.; Nishimura, T.; Saito, Y.; Ozawa, S.; et al. Identification of novel alternative splice variants of human constitutive androstane receptor and characterization of their expression in the liver. *Mol. Pharmacol.* **2004**, *65*, 496–502. [CrossRef]

69. Jamis-Dow, C.A.; Katki, A.G.; Collins, J.M.; Klecker, R.W. Rifampin and rifabutin and their metabolism by human liver esterases. * Xenobiotica 1997*, *27*, 1015–1024. [CrossRef]

70. Ross, M.K.; Crow, J.A. Human carboxylesterases and their role in xenobiotic and endobiotic metabolism. *J. Biochem. Mol. Toxicol.* **2007**, *21*, 187–196. [CrossRef] [PubMed]

71. Wang, D.; Zou, L.; Jin, Q.; Hou, J.; Ge, G.-B.; Yang, L. Human carboxylesterases: A comprehensive review. *Acta Pharm. Sin. B* **2018**, *8*, 699–712. [CrossRef] [PubMed]

72. Merali, Z.; Ross, S.; Paré, G. The pharmacogenetics of carboxylesterases: CES1 and CES2 genetic variants and their clinical e

73. Fukami, T.; Yokoi, T. The emerging role of human esterases. *Drug Metab. Pharmacokinet.* **2012**, *27*, 466–477. [CrossRef]

74. Andaoro, C.; Koorsen, G.; Knight, J.C.; Bornman, L. Vitamin D receptor gene methylation is associated with ethnicity, tuberculosis, and TaqI polymorphism. *Hum. Immunol.* **2010**, *72*, 262–268. [CrossRef]

75. Zmuda, J.M.; Cauley, J.A.; E Ferrell, R. Molecular epidemiology of vitamin D receptor gene variants. *Epidemiol. Rev.* **2000**, *22*, 203–217. [CrossRef]

76. Jurutka, P.W.; Remus, I.S.; Whitfield, G.K.; Thompson, P.D.; Hsieh, J.C.; Zitzer, H.; Tavakkoli, P.; Galligan, M.A.; Dang, H.T.; Haussler, C.A.; et al. The polymorphic N terminus in human vitamin D receptor isoforms influences transcriptional activity by modulating interaction with transcription factor IIB. *Mol. Endocrinol.* **2000**, *14*, 401–420. [CrossRef]

77. Shaik, A.P.; Alsaeed, A.H.; Alsaeed, M.A.; Alyousef, A.; Bammidi, V.K.; Sultana, A. Vitamin D Receptor FokI, Apal and TaqI polymorphisms in lead exposed subjects from Saudi Arabia. *Front. Genet.* **2019**, *10*, 388. [CrossRef]
80. Vieira, L.A.; De Marchi, P.L.; Dos Santos, A.A.; Christofolini, D.M.; Barbosa, C.P.; Fonseca, F.L.A.; Bianco, B.; Rodrigues, L.M.R. Analysis of FokI polymorphism of vitamin D Receptor gene in intervertebral disc degeneration. *Genet. Test. Mol. Biomark.* 2014, 18, 625–629. [CrossRef]

81. DeLuca, H.F. Evolution of our understanding of vitamin D. *Nutr. Rev.* 2008, 66, S73–S87. [CrossRef]

82. Sakaki, T.; Sawada, N.; Komai, K.; Shiozawa, S.; Yamada, S.; Yamamoto, K.; Ohyama, Y.; Inouye, K. Dual metabolic pathway of 25-hydroxyvitamin D3 catalyzed by human CYP24. *J. Biol. Inorg. Chem.* 2000, 267, 6158–6165. [CrossRef] [PubMed]

83. Penna-Martinez, M.; Ramos-Lopez, E.; Stern, J.; Kahles, H.; Hinsch, N.; Hansmann, M.-L.; Selkinski, I.; Grünwald, F.; Vorländer, C.; Bechstein, W.O.; et al. Impaired vitamin D activation and association with CYP24A1 haplotypes in differentiated thyroid carcinoma. *Thyroid* 2012, 22, 709–716. [CrossRef] [PubMed]

84. Bailey, R.; Cooper, J.D.; Zeitels, L.; Smyth, D.; Yang, J.H.; Walker, N.; Hyppönen, E.; Dunger, D.; Ramos-Lopez, E.; Badenhoop, K.; et al. Impaired vitamin D metabolism and association with CYP24A1 haplotypes in differentiated thyroid carcinoma. *Thyroid* 2012, 22, 709–716. [CrossRef] [PubMed]

85. Rinkwitz, S.; Geng, F.; Manning, E.; Suster, M.; Kawakami, K.; Becker, T.S.T.S. BAC transgenic zebrafish reveal hypothalamic enhancer activity around obesity associated SNP rs9939609 within the humanFTOgene. *Genesis* 2015, 53, 640–651. [CrossRef]

86. Seo, S.; Takayama, K.; Uno, K.; Ohi, K.; Hashimoto, R.; Nishizawa, D.; Ikeda, K.; Ozaki, N.; Nabeshima, T.; Miyamoto, Y.; et al. Functional analysis of deep intronic SNP rs13438494 in intron 24 of PCLO gene. *PLoS ONE* 2013, 8, e76960. [CrossRef] [PubMed]

87. Rose, K.; Penna-Martinez, M.; Klahold, E.; Karger, D.; Shoghi, F.; Kahles, H.; Bayer, M.; Hintermann, E.; Pfeilschifter, J.M.; Badenhoop, K.; et al. Influence of the vitamin D plasma level and vitamin D-related genetic polymorphisms on the immune status of patients with type 1 diabetes: A pilot study. *Clin. Exp. Immunol.* 2013, 171, 171–185. [CrossRef]

88. Jin, C.H.; Pike, J.W. Human vitamin D receptor-dependent transactivation in Saccharomyces cerevisiae requires retinoid X receptor. *Mol. Endocrinol.* 1996, 10, 196–205.

89. Väisänen, S.; Dunlop, T.W.; Sinkkonen, L.; Frank, C.; Carlberg, C. Spatio-temporal activation of chromatin on the human CYP24 gene promoter in the presence of 1α,25-dihydroxyvitamin D3. *J. Mol. Biol.* 2005, 350, 65–77. [CrossRef] [PubMed]

90. Roff, A.; Wilson, R.T. A novel SNP in a vitamin D response element of the CYP24A1 promoter reduces protein binding, transactivation, and gene expression. *J. Steroid Biochem. Mol. Biol.* 2008, 112, 47–54. [CrossRef] [PubMed]

91. Hibler, E.; Klimentidis, Y.C.; Jurutka, P.; Kohler, L.N.; Lance, P.; Roe, D.J.; Thompson, P.A.; Jacobs, E.T. CYP24A1 and CYP27B1 polymorphisms, concentrations of vitamin D metabolites, and odds of colorectal adenoma recurrence. *Nutr. Cancer* 2015, 67, 1131–1141. [CrossRef] [PubMed]

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).