Andexanet Alfa: The First Factor Xa Inhibitor Reversal Agent

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Direct factor Xa (FXa) inhibitors, also known as direct oral anti-coagulants (DOACs), have a wide range of indications to prevent and treat thrombotic complications. DOACs have several advantages over widely used vitamin K antagonists (e.g., warfarin), including fewer monitoring requirements, comparable efficacy, and lower rates of severe bleeding.[1] The annual rate of major bleeding in patients with atrial fibrillation taking FXa inhibitors is about 2.1-3.5% which is lower than warfarin. However, a limitation for DOAC use, especially for patient comfort, is the previous lack of an effective reversal agent for acute bleeding episodes.[2] A reversal agent is currently approved for dabigatran, idarucizumab, but it is not effective at reversing bleeding for FXa inhibitor DOACs such as apixaban and rivaroxaban. Currently, fresh frozen plasma, prothrombin-complex concentrate, and recombinant VIIa are used for reversing apixaban and rivaroxaban however these are non-specific options and their effectiveness have not been established in blinded clinical trials. As the number of patients switching from warfarin to DOACs increases, the need for an effective reversal agent rises.[3]

Andexanet alfa (AndexXa®) reverses FXa anticoagulation activity. It received conditional FDA approval in 2018 to treat patients taking apixaban or rivaroxaban for life-threatening or uncontrolled bleeding. The conditional approval was granted by the FDA after interim results from the ANNEXA-4 trial were published, full approval by the FDA for the indication is contingent on the completion of the trial. The purpose of this article is to review the available clinical trial data for andexanet alfa and evaluate its efficacy and safety.

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PHARMACOLOGY

Mechanism of Action

Andexanet alfa is a recombinant modified variant of human FXa. It competes with endogenous FXa as a target for anti-FXa inhibitors and temporarily reduces the anticoagulant activity of such inhibitors. FXa possesses coagulant activity by forming a prothrombinase complex that cleaves prothrombin to thrombin. Andexanet alfa is modified, allowing it to bind to direct FXa inhibitors but not cleave prothrombin to thrombin. Therefore, it does not exhibit the normal pro-coagulant activity of endogenous FXa, an important clinical concern.

Pharmacodynamics and Pharmacokinetics

Multiple markers for the effect of andexanet alfa exist, including anti-FXa activity, unbound plasma FXa concentration, and thrombin generation. Change in anti-FXa activity is the primary marker used in andexanet alfa approval trials. In the anti-FXa assay, plasma samples containing FXa inhibitor are exposed to an excess of FXa; the remaining FXa activity is then measured.[4] Andexanet alfa is administered as an IV bolus followed by an additional 2 hour infusion. It has a quick onset, reducing anti-FXa activity within 2 minutes of the completion of bolus. Baseline anti-FXa activity is measured before administration of andexanet alfa, and measured again 2-5 minutes after end of andexanet alfa bolus completion. Andexanet alfa retains suppression of anti-FXa activity throughout infusion, and returns to placebo level approximately 2 hours after the end of infusion.[5] The infusion time of 2 hours was chosen as the expected time to achieve a definitive hemostatic plug.[6]

Andexanet alfa does not neutralize FXa inhibitors; the reduction in activity is temporary. While anti-FXa activity was used in the trials, monitoring of DOACs through anti-FXa activity or other biomarkers is not routinely performed in clinical practice. The assay is primarily used for unfractionated heparin (UFH) and low-molecular weight heparin (LMWH) and was adopted for use in the trials.[7] Clinical indication for andexanet alfa is based upon history of taking rivaroxaban or apixaban, patients should not be excluded on the basis of normal coagulation biomarkers.

Andexanet alfa has been shown to increase thrombin potential above baseline; however, the precise mechanism is not yet clearly understood. Andexanet alfa is catalytically inactived and has not been shown to have pro-thrombotic activity. Andexanet alfa has been shown to inhibit tissue factor pathway inhibitor (TFPI), an endogenous inhibitor of FXa. Animal models have suggested that the binding of andexanet alfa to TFPI does not affect hemostasis.[8] Currently, little is known about the metabolism and excretion of andexanet alfa. Table 1 contains a summary of andexanet alfa's pharmacokinetic properties.

CLINICAL TRIALS

Andexanet alfa was approved for use in the reversal of apixa-

Table 1 | Andexanet Alfa Pharmacokinetics[9]

Parameters	Value
C_{max}	~90 mcg/mL
T_{max}	~17 min
AUC	~210 mcg*h/mL
$t_{1/2}$	5-7 hours
CL	4.3 L/hour
V_d	5 L

Values presented are averages. **AUC** = area under the curve; C_{max} = maximum concentration; **CL** = clearance; $t_{1/2}$ = elimination half life; t_{max} = time to C_{max} ; V_d = volume of distribution

ban and rivaroxaban related major bleeding in May 2018. It was given breakthrough and fast track approval status from the FDA on the basis of Phase II and III trials that demonstrated a decrease in anti-factor Xa activity from baseline in healthy patients. The ongoing ANNEXA-4 trial evaluates the safety and efficacy of andexanet alfa in patients with acute major bleeding.

Phase II Trial

Siegal et al. conducted a phase II trial to evaluate the safety of andexanet alfa as well as look into the PK, and PD parameters in subjects that were treated with apixaban.[9] Healthy patients without an indication for apixaban and aged between 18-45 years were included. Exclusion criteria included any personal or family history of hypercoagulability or clotting. Each subject received apixaban 5 mg orally every 12 hours for 5.5 days. A total of 54 subjects were randomized to receive either andexanet alfa or placebo in a 2:1 ratio. Each group was furthered divided into 6 different dosing cohorts comprised of either (i) 90 mg IV bolus, (ii) 210 mg IV bolus, (iii) 420 mg IV bolus, (iv) 420 mg IV bolus plus 180 mg infusion over 45 minutes, (v) 420 mg IV bolus plus 180 mg bolus 45 minutes after the first bolus, (vi) 420 mg IV bolus plus 480 mg infusion over 120 minutes (n=8 for each group). Subjects were followed for 48 days after treatment.

The primary pharmacodynamics outcome was anti-FXa activity with all dosing regimens significantly reducing anti-FXa activity compared to placebo. Reduction was greatest in the 420 mg bolus groups (92.8% to 95.0% decrease in anti-FXa activity relative to baseline; P< 0.05), 2 minutes after bolus was administered. Placebo saw a mean anti-FXa activity decrease of 7.1% (SD = 10.8%). Anti-FXa activity returned to placebo levels within 1-2.5 hours after a single bolus administration. In the bolus plus infusion or multiple bolus administration cohorts, it took 3.3-4.3 hours to return to placebo levels. Infusion after bolus (cohort 4 and 6) resulted in sustained anti-FXa decrease (3.5 to 3.75 hours; P< 0.05 vs placebo). Sustained reduction in anti-FXa activity of the infusion cohorts was used in determining administration of andexanet alfa in subsequent trials.

Thrombin generation, a secondary outcome, decreased with apixaban administration and was restored within 2 minutes of apixaban bolus. Restoration of thrombin generation was measured as the percentage of subjects that returned to thrombin levels within 1 SD of the population mean before apixaban administration. In dosing cohort 1 thrombin was restored in 67% of subjects, cohort 2: 83% of subjects, cohort 3: 100% of subjects, cohort 4: 100% of subjects, cohort 5: 83% of subjects, cohort 6:

100% of subjects. In placebo, restoration of thrombin generation occurred in 6% of subjects. Thrombin generation increased above baseline for the highest bolus dose 420 mg (cohort 3), but not for the bolus plus infusion (cohort 4 and 6).

ANNEXA-A and ANNEXA-R

ANNEXA-A and ANNEXA-R were parallel phase III clinical trials to determine the safety and efficacy of andexanet alfa to reverse anticoagulation in older healthy volunteers taking either apixaban or rivaroxaban.[8] The trials were randomized, double-blinded, and placebo-controlled. A total of 145 healthy participants, without active bleeding, aged 50 to 75 were randomly assigned to either the apixaban group in a 3:1 ratio of drug (n=48) to placebo (n=17) or rivaroxaban in a 2:1 ratio of drug (n=53) to placebo (n=27). Participants first received either 5 mg of apixaban orally twice daily for 3.5 days or 20 mg of rivaroxaban orally for 4 days to achieve steady-state plasma levels. In the apixaban group participants received either a single bolus dose of andexanet alfa 400 mg or a 400 mg bolus dose plus 480 mg infused over 120 minutes. In the rivaroxaban group participants received a higher dose of andexanet alfa, either a single bolus dose of andexanet alfa 800 mg or an 800 mg bolus dose plus 960 mg infused over 120 minutes.

The primary study end point was percent change in anti-FXa activity. The change in anti-FXa activity was measured as the change from baseline (before andexanet alfa administration) to the nadir, defined as the lowest value at either 2 minutes or 5 minutes after the end of bolus, or 10 minutes before or 5 minutes after the end of infusion. In the apixaban bolus only group, andexanet alfa reduced anti-FXa activity from baseline by a mean 94±2% compared to 21±9% for placebo (no andexanet alfa) (P<0.001). In the rivaroxaban group anti-FXa activity reduction from baseline was 92±11% vs. 18±15% for placebo (P<0.001). In the bolus plus infusion groups, anti-FXa activity from baseline was reduced 92±3% in the apixaban group vs. 33±6% for placebo (P<0.001); and 97±2% in the rivaroxaban group vs. 45±12% for placebo (P<0.001). Anti-FXa activity persisted for 1-2 hours after both bolus and infusion andexanet alfa administration and gradually increased to levels similar to placebo consistent with clearance of the DOAC.

Secondary efficacy endpoints included change in thrombin generation which increased significantly in both the bolus and infusion arms of the apixaban and rivaroxaban study (p<0.001 for both comparisons to placebo).

ANNEXA-4

ANNEXA-4 is an ongoing, prospective, open-label study investigating the use of andexanet alfa in patients undergoing acute major bleeding. The study is due to complete in November 2022. An interim report on 67 patients was reported which will be used in this review.[2] There were no active comparator or placebo groups. However, the use of additional coagulation intervention such as plasma or prothrombin complex was allowed if warranted. Safety data was collected in all patients, while efficacy analysis was only applied to patients that had baseline anti-FXa activity greater than 75 ng/mL and met the criteria of acute major bleeding. Of the total 67 patients included, 19 did not meet the efficacy population inclusion criteria due to insufficiently low baseline anti-FXa activity. The two primary outcomes were the percent of patients achieving excellent or good hemostatic efficacy 12 hours after andexanet alfa administration and percent change in anti-FXa activity, measured at various points up to 12 hours after comple-

tion of infusion.

Inclusion criteria included adults at least 18 years old who had received an anti-FXa inhibitor (apixaban, rivaroxaban, edoxaban, or enoxaparin) within the past 18 hours at the time of acute major bleeding. All patients had a history of thrombotic events and cardiovascular disease. Most patients were taking either rivaroxaban (32 of 67 patients; median daily dose 20 mg) or apixaban (31 of 67 patients; median daily dose 5 mg); 4 patients were taking enoxaparin. Acute major bleeding was defined as either potentially life-threatening acute overt bleeding with signs or symptoms of hemodynamic compromise; acute overt bleeding associated with a decrease in hemoglobin of at least 2 g/dL or a hemoglobin level of 8 g/dL or less if no baseline was available; or acute symptomatic bleeding in a critical area or organ. The primary sites of bleeding were gastrointestinal (49% of patients) and intracranial (42% of patients). The mean time from presentation to the emergency department to initiation of andexanet alfa was 4.8±1.9 hours.

Exclusion criteria included scheduled surgery within 12 hours after presentation (excluding minimally invasive surgery); intracranial hemorrhage in a patient with Glasgow Coma Scale score less than 7; intracerebral hematoma with estimated volume greater than 60 mL; expected survival of less than 1 month; occurrence of a major thrombotic event in the past 2 weeks; or receiving either vitamin K antagonist, dabigatran, prothrombin complex concentrate, or whole blood or plasma in the past 7 days. Patients that took apixaban or rivaroxaban more than 7 hours before the administration of andexanet alfa received the low dose andexanet alfa 400 mg bolus over 15-30 minutes + 480 mg infusion over 2 hours; patients who had taken enoxaparin, edoxaban, or rivaroxaban 7 hours or less before the administration of the bolus dose or at an unknown time received the high dose 800 mg bolus over 15-30 minutes + 960 mg infusion over 2 hours.

Hemostatic outcomes were adjudicated by an independent committee on the basis of pre-determined criteria for each type of bleed. Intracranial hemorrhage was assessed by change in volume from baseline, an increase of no greater than 20% from baseline at hour 1 and 12 was considered excellent hemostasis; an increase no greater than 35% from baseline at hour 12 was considered good hemostasis. Nonvisible bleeding, including gastrointestinal bleeding, was assessed by change in corrected hemoglobin and hematocrit from baseline. At 12 hours, a decrease of no more than 10% was considered excellent; a decrease of no more than 20% and administration of no more than 2 units of additional coagulation intervention products was considered good. Visible bleeding was assessed by time for cessation of bleeding. Cessation within 1 hour after infusion was considered excellent; cessation within 4 hours and no need for additional coagulation intervention was considered good. Hemostatic efficacy of excellent or good was seen in 37 of 47 patients (79%; 95% CI, 64% to 89%), with the hemostasis of 31 patients considered excellent and 6 patients considered good.

For the most common types of bleeding, excellent or good efficacy was seen in 84% for gastrointestinal bleeding and 80% for intracranial bleeding. Nine patients were considered to have poor or no hemostatic efficacy. Of those, 4 were taking apixaban and 5 were taking rivaroxaban. Types of bleeding varied, 3 had gastrointestinal bleeding, 4 intracranial bleeding, and 2 other. Modified Rankin scale (scored from 0 (no symptoms or disability) to 6 (death)) for patients with intracranial bleeding were 2.2±1.9 at baseline and 2.0±2.0 at 30 days among the survivors. One patient received a plasma infusion and another received a platelet infusion before andexanet alfa treatment. After andexanet alfa treatment, 4

Table 2 | Anti-Factor Xa Activity Reduction from Baseline[2,8]

Trial	Initial Anticoagulant	Intervention	Primary Outcome
ANNEXA-A	Apixaban 5 mg BID	- Andexanet 400 mg bolus (n=24) -vs- - Placebo (n=17)	94±2% vs 21±9% P<0.001[a]
		- Andexanet 400 mg bolus + 480 mg infusion (n=24) -vs- - Placebo (n=27)	92±3% vs 33±6% P<0.001[a]
ANNEXA-R	Rivaroxaban 20 mg QD	- Andexanet 800 mg bolus (n=27) -vs- - Placebo (n=27)	92±11% vs 18±15% P<0.001[a]
		- Andexanet 800 mg bolus + 960 mg infusion (n=27) -vs- - Placebo (n=27)	97±2% vs 45±12% P<0.001[a]
ANNEXA-4	Apixaban (n=20), rivaroxaban (n=26), or enoxaparin (n=1)	**Anticoagulation >7 hours:** - Andexanet 400 mg bolus + 480 mg infusion **Anticoaguatlion ≤7 hours:** - Andexanet 800 mg bolus + 960 mg infusion	Excellent or good hemostasis[b]: 79% (95% CI, 64-89)

a: The primary end point was the percent change in anti-factor Xa activity from baseline to nadir. The nadir was defined as 2 or 5 minutes after the end of the bolus, or 10 minutes before to 5 minutes after the end of the infusion.
b: Hemostasis definitions: intracranial hemorrhage increase in volume of 20% or less from baseline at both 1 hour and 12 hours after infusion was considered to be excellent hemostasis, whereas an increase in volume of 35% or less from baseline at 12 hours was considered to be good. Nonvisible bleeding (i.e gastrointestinal bleeding) was evaluated on corrected hemoglobin levels and hematocrit at 12 hours compared to baseline. A decrease in both hemoglobin and hematocrit of less than 10% considered to be excellent and a decrease of 20% or less and with the administration of no more than two units of additional coagulation intervention considered to be good. Patients with poor or no hemostatic efficacy: rivaroxaban n=5 and apixaban n=4

patients received plasma, tranexamic acid, or platelets.

For the 26 patients that received rivaroxaban, the median decrease of anti–FXa activity from baseline at the end of bolus was 89% (95% CI, 58% to 94%); at the end of the 2-hour infusion, 86% (95% CI, 55% to 93%). For the 26 patients that received apixaban the median decrease of anti–FXa activity from baseline at the end of bolus was 93% (95% CI, 87% to 94%); at the end of the 2-hour infusion, 92% (95% CI, 85% to 94%). Refer to Table 2 for a summary of the reduction in anti-FXa from Phase III and IV clinical trials.

The ANNEXA-4 study is still ongoing and is therefore not adequately powered for its efficacy endpoints. A total of 47 patients were assessed for efficacy endpoints, and 67 for safety endpoints. The study will continue enrolling patients until efficacy data is available for 162 patients. This would result in an expected 230 patients for safety data. Additional data is required to establish a relationship between reduction in anti-FXa levels and hemostatic outcomes. The final publication should shed light on whether these efficacy and safety results are greater or less than expected for patients receiving andexanet alfa.

ADVERSE EFFECTS

Andexanet alfa is generally well tolerated. The most common events are general disorders and mild infusion site reactions. In the phase I and II trials infusion reactions occurred in 19.4% of subjects vs 11% in placebo. All reactions that occurred were considered mild and may have included facial flushing, nonproductive cough, dyspnea, and abnormal taste during infusion.

Andexanet alfa has a black box warning for thromboembolic risk, ischemic risks, cardiac arrest, and sudden deaths. In the ongoing ANNEXA-4 trial thrombotic events occurred in 12 patients including 1 patient with myocardial infarction, 5 with stroke, 7 with deep-vein thrombosis, and 1 with pulmonary embolism. Some patients had more than one event. Thrombotic events occurred within 3 days of andexanet alfa treatment in 4 patients, the remaining events occurred between days 4 and 30. Ten deaths occurred, 6 were classified as CV related, 4 non-CV related. Anticoagulation was resumed in 18 patients within the 30 day observation period. The ANNEXA-4 trial does not have a placebo or comparator group, therefore it is unknown whether andexanet alfa treated patients experienced these serious events at a higher or lower rate than would be observed for non-specific reversal agent or placebo.

In the trials no antibodies to factor X, FXa, or neutralizing antibodies to andexanet alfa were observed. A transient elevation in the coagulation marker D-dimer has been observed, suggesting the possibility of pro-thrombotic activity. Increases in D-dimer may be explained by andexanet alfa binding to endogenous anti-FXa, tissue factor pathway inhibitor (TFPI). Studies have indicated that decrease in TFPI are not necessarily associated with developing thrombotic events.[10]

DOSING AND ADMINISTRATION

Andexanet alfa is only indicated for the reversal of anticoagulation in patients treated with apixaban or rivaroxaban. Mechanistically andexanet alfa would be expected to have activity against other DOACs such as betrixaban and edoxaban, however current trial data is limited to apixaban and rivaroxaban. Andexanet alfa is given by IV administration, in an IV bolus plus 2-hour infusion.

Rate of bolus infusion is 30 mg/min. Dosing regimen is determined by FXa inhibitor, FXa inhibitor dose, and time since last FXa inhibitor dose. Data for renal or hepatic adjustment is not available. For patients who are receiving rivaroxaban ≤10 mg or apixaban ≤5 mg, andexanet alfa is administered as a 400 mg bolus followed by a 480 mg infusion at a rate of 4 mg/min for 120 minutes. For patients receiving rivaroxaban >10 mg (or unknown) or apixaban >5 mg (or unknown), andexanet alfa is administered as an 800 mg bolus followed by a 960 mg infusion at 8 mg/min for 120 minutes.

COST AND AVAILABILITY

Andexanet alfa is supplied in cartons of four single-use 100 mg vials. Pricing data is $3300 for 100 mg.[5] Low dose reversal requires 9 vials, totaling $29,700; high dose reversal requires 18 vials, totaling $59,400. For comparison, human prothrombin complex concentrate (Kcentra®) costs approximately $5000 per treatment depending on pre-treatment INR and body weight.

Since AndexXa® became available on the market in July 2018 its availability has been limited. The manufacturer of AndexXa®, Portola Pharmacueticals™, is awaiting FDA approval of a larger scaled manufacturing process "Generation 2" to meet the supply demands.

SUMMARY

The approval of andexanet alfa as the only FXa inhibitor reversal agent has been long anticipated. Initial trials have shown efficacy in reducing anti-FXa activity as well as few adverse effects. Continued approval of andexanet alfa is contingent on the hemostasis results of trials such as ANNEXA-4. While ANNEXA-4 has shown positive results for hemostatic efficacy in a small number of patients, limitations exist. However, despite thromboembolic safety concerns which are present on current VKA reversal agents, andexanet alfa is the only reversal agent available for apixaban and rivaroxaban. Further clinical trial results and real-world data will likely solidify andexanet alfa's place in clinical practice.

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PERSONALIZED MEDICINE CORNER

Effect of Phenoconversion on Clinical Pharmacogenetics: Patient Case

The University of Florida Health Pharmacogenetics Consult Clin-ic incorporates pharmacogenetic data into drug therapy recom-mendations. In this article, we describe a clinic encounter with a patient whose genotype-predicted phenotype was altered by con-comitant drug therapy.[1]

Patient Presentation

A 54 year-old woman with a history of depression, generalized anxiety disorder, neuropathic pain, diabetes, fibromyalgia and poor response to antidepressant therapy underwent pharmaco-genetic testing. Her medications included bupropion, duloxetine, and tramadol. The patient reported constipation and worsening gastrointestinal symptoms with tramadol, but no pain relief. Previ-ous antidepressant use included high-dose citalopram and escital-opram with no effectiveness.

Pharmacogenetic Test Results

Her genotypes were *CYPC19*1/*17* - associated with increased cytochrome P450 2C19 (CYP2C19) enzyme activity and the rapid metabolizer phenotype; and *CYP2D6*1/*4* - associated with nor-mal CYP2D6 enzyme activity and the normal metabolizer pheno-type.

Impact of Concomitant Drug Therapy on Enzyme Activity and CYP2D6 Phenotype

Duloxetine and bupropion are classified by the FDA as moderate and strong CYP2D6 inhibitors, respectively. These agents can "phenoconvert" patients with a normal *CYP2D6* genotype to present as intermediate (with moderate inhibitors) or poor (with strong inhibitors) metabolizers. Thus, the patient would be a CYP2D6 poor metabolizer after considering her drug therapy.

Applications to Drug Therapy

Citalopram and escitalopram are inactivated by the CYP2C19 enzyme. Presence of the rapid metabolizer CYP2C19 phenotype is associated with lower plasma concentrations and a higher risk of treatment failure with these agents. In this patient, her CYP2C19 phenotype likely contributed to her previous poor re-sponse to these agents.[2]

Tramadol is biotransformed by the CYP2D6 enzyme to a more active metabolite, with approximately 200-fold greater affinity for the opioid mu receptor than the parent compound. Her CYP2D6 poor metabolizer phenotype (as a result of phenoconversion) can lead to decreased biotransformation of tramadol to its more active form, thereby increasing the likelihood of inadequate pain relief.[3,4] This may also contribute to serotonergic excess in this patient secondary to tramadol's inhibition of serotonin reuptake[3] in com-bination with treatment with duloxetine, a serotonin reuptake inhibitor.

Genotype-Guided Drug Therapy Recommendations

For depression, we recommended avoiding future use of CYP2C19-mediated antidepressants (i.e., sertraline) because of this patient's rapid CYP2C19 metabolism status. Alternative treat-ment options include discontinuing bupropion and/or duloxetine and starting fluoxetine or desvenlafaxine, neither of which are significantly affected by genetic variability in the CYP2C19 or CYP2D6 enzymes.

For pain management, if the patient is maintained on bupropion or duloxetine, we recommended discontinuation of tramadol and use of an alternative agent not affected by CYP2D6 (e.g., NSAID, morphine). If the current CYP2D6 inhibitors are discontinued, the patient's response to tramadol would be expected to improve.

Discussion

In addition to having a pharmacogenetic variant causing rapid CYP2C19 activity, treatment choices in this patient were compli-cated by her phenoconversion to a CYP2D6 poor metabolizer secondary to drug-drug interactions. While phenoconversion is often caused by concomitant medication use as in this case, it can also be a result of non-drug factors such as certain diseases (e.g., liver disease, cancer).[1]

The clinical impact of phenoconversion can be difficult to predict and depends on the patient's genotype, affected enzyme(s), and concomitant medications.[3,5] For example, patients with a de-creased-function genotype (e.g., CYP2D6 intermediate metaboliz-ers) are thought to be most susceptible to clinically relevant ef-fects of drug-induced enzyme inhibition due to the presence of a lower baseline enzyme function. However, patients classified as poor metabolizers have no existing enzyme function and are therefore not susceptible to further drug-induced enzyme inhibi-tion.[1]

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