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Case Report

Bezafibrate Appropriateness towards Deprescribing- A Case Report on a Clinical Pharmacist Intervention

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Abstract

Hypertriglyceridemia (HTG) incidence as a contributing factor to high cardiovascular risk is elevating, the cornerstone of treatment is based on low-fat diet in combination with intensified statins therapy. Adding Fibric acid derivatives such as Bezafibrate is considered when moderate to severe triglycerides levels hits, measured as above 500 mg/dL or 5.65 mmol/L. Proper prescribing of Bezafibrate is crucial since it can aggravate side effects such as muscle and hepatic toxicity, especially in renal impairment. Moreover, the sustained-release (SR) formulation of Bezafibrate is not recommended in patients with creatinine clearance (CrCl) below 60 milliliters/minute (mL/min). We report a clinical pharmacist intervention regarding the appropriateness of Bezafibrate prescribing in inpatients relying on recent guidelines and adjustment to renal function. In four months review, Twenty-nine out of thirty-two reviewed Bezafibrate orders were stopped, eleven were contraindicated. Evaluation of Bezafibrate efficacy, safety and necessity should be an ongoing process by physicians.

Keywords: Bezafibrate; Clinical Pharmacist Intervention; Appropriateness; Cholangitis

Introduction

Bezafibrate is a long-established treatment to achieve a considerable decrease in triglycerides (TG) levels, up to 50%, in patients with primary, secondary and mixed hypertriglyceridemia (HTG) [1,2].

It acts mainly by activating peroxisome proliferator-activated receptor alpha (PPARα), an intracellular receptor that expressed intensively in tissues with high fatty oxidation rate such as liver, kidneys and heart muscle [3]. PPARα controls a set of regulation genes responsible for lipid catabolism that leads to increased high-density lipoprotein cholesterol synthesis, TG reduction and stimulation of reverse cholesterol transport [3,4].

The treatment potential of fibric acid derivatives such as Bezafibrate for HGT still shown in patients with moderate HGT (TG serum levels 500 to 999 mg/dL or 5.65 to 11.3 mmol/L) and severe HGT (TG serum levels ≥ 1000 mg/dL or ≥ 11.3 mmol/L). [5]

Those whom benefit from consideration of such treatment are adults aged 20-39 years old in combination with emphasized low-fat diet, adults aged 40-75 years old with 10-year atherosclerotic cardiovascular disease (ASCVD) score ≥ 5%, ASCVD or Type-2 diabetes mellitus (T2DM) in combination with intensified statins therapy and emphasized low-fat diet to reduce the risk of pancreatitis [6]. Fibric acid derivatives such as Bezafibrate are not indicated for mild to moderate HGT (TG serum levels 150 to 499 mg/dL or 1.7 to 5.6 mmol/L). [6]

In addition to different types of HGT as an approved indication, Bezafibrate is used as an off-label to improve biochemical parameters and symptoms such as pruritus in patients with primary biliary cholangitis and primary sclerosing cholangitis [7]. Standard dosing is 200 mg three times daily for the immediate release formulation or as effectively 400 mg once daily for the sustained release (SR) formulation [8]. Based of pharmacokinetic

studies, Bezafibrate is eliminated rapidly and almost exclusively by the kidneys and, therefore, renal dose adjustment is incumbent by prescribers due to drug accumulation and toxic effect [9].

In patients with creatinine clearance (CrCl) below 60 milliliters/minutes (mL/min), the SR formulation is not recommended and even contraindicated and must be replaced with the immediate release formulation [10]. Polanco, et al. [11] demonstrated that fibric acid derivatives could induce acute renal failure with a noted percentage of patients treated whom not recovered their basic renal function. Additionally, Zingerman, et al. [12] showed that Bezafibrate cessation increased CrCl in chronic kidney disease patients.

We aim to report the impact of a real time clinical pharmacist intervention regarding the appropriateness of Bezafibrate treatment in inpatients according to updated treatment guidelines and consideration of renal function.

Methods

Intervention population, Inclusion and exclusion criteria

Inpatients in Tel-Aviv SOURASKY Medical Center, Israel hospitalized in all hospital wards treated with Bezafibrate whether as a continued treatment from community medical clinics or initiated during hospitalization from May 2023 until August 2023. All ages and genders were included, no exclusion criteria.

Data was drawn from a server reporting service developed by the computing department of the medical center that can extract all medication orders prescribed and administered as documented in the patients' medical file program " Chameleon ". Illimitable filtering by date, medication and ward was available. During a four months period, thirty-two medical records reviewed

Intervention design

Assigned baseline characteristics for a clinical pharmacist intervention were arranged in an Excel document template as shown in (Table 1).

Parameter	
Males (n)	23
Females (n)	9
Age (years), Average	66.47
CrCl (mL/min), average	76.65
Serum TG level (mg/dL), average	197.4
T2DM (%)	71.88
On non-intensified statins therapy (%)	56.25

Table 1: Baseline Patients Characteristics, n: 32.

A clinical pharmacist proactive counseling was documented in an allocated field in the "Chameleon" program visible to all medical staff. A follow-up by a clinical pharmacist regarding physicians' responsiveness for the counselling was done in the same day or the next day uttermost. Our study is considered a retrospective on existing data without inclusion of patients, no informed consent needed and was approved by the institutional ethical committee according to the principles of the Declaration of Helsinki.

Results

The majority of the patients were prescribed 400 mg once daily from the SR formulation of Bezafibrate and approximately 34% of them were with an estimated CrCl less than 60 mL/min. Nearly 38% of the patients were hospitalized in the numerous internal medicine departments. Three patients were prescribed Bezafibrate for an off-label indication and all twenty-nine prescribed orders were halted according to clinical pharmacist documented counselling, eleven prescriptions were contraindicated (Figure 1).

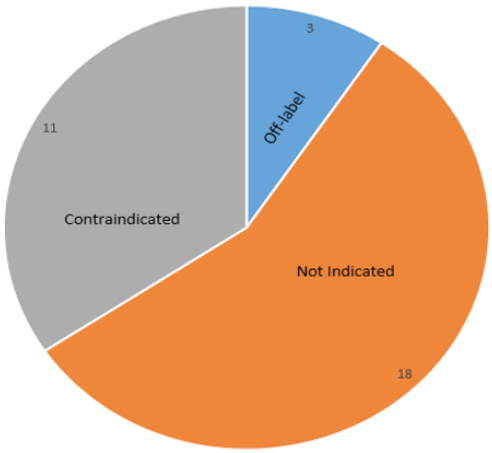

Figure 1: Bezafibrate appropriateness.

Discussion

The prevalence of HGT has been climbing in recent decades similar to T2DM and obesity. [13] Its clinical significance accentuated when it relates to the increased risk for ASCVD [14]. Physiologically, TG-rich lipoproteins including chylomicrons, very low-density lipoproteins, and their residues are the main transporters of circulating TG, levels above 150 mg/dL or 1.7 mmol/L indicate high cardiovascular risk and impel clinicians to consider other factors whether dependent or not [15]. Expectedly, most of the medical records reviewed in our study were also patients with T2DM; this complies with the atherogenic lipid profile theory in which HGT is a substantial component [16]. Parallelly, chronic kidney disease patients tend to have HGT

mainly because of delayed catabolism of high TG lipoproteins along with increased production of such lipoproteins by the liver [17]. Innately, some healthcare professionals prescribe Bezafibrate for HGT without meticulous familiarity with the recent guidelines and unfortunately, without regard to current renal function of the patient.

In December 2010, The European Medicines Agency's Committee for Medicinal Products for Human Use recommended that healthcare professionals should not prescribe fibric acid derivatives to newly diagnosed HGT patients as first-line treatment, except for those with severe HGT or those who cannot take statins [18]. None of our cohort reviewed and intervened were diagnosed with severe HGT and slightly above half were taking non-intensified statins therapy which is inconsistent with recent guidelines. In our review, 34% of the Bezafibrate SR formulation prescribed was contraindicated due to CrCl below 60 mL/min, and 56.25% was inappropriately indicated based on TG levels. This, by our evaluation, could be attributed to physicians' focus on hospitalization reason, which was not due HGT complications, rather than on continued inpatients treatment in addition to low hospitalization days that do not allow a thorough review for all medical record.

Moreover, much concern on such patients was highlighted. Because, according to Charach, et al. [19] Bezafibrate is demonstrated as a common cause for serum creatinine elevation and renal function deterioration, this can affect elimination of other medication as most of patients is polypharmic and exacerbate renal related conditions. Such deterioration can be elaborated by reduced renal perfusion via afferent glomerular blood vessel, impairing nephron proximal tubules and induced acute kidney injury due to rhabdomyolysis [12]. In Australia, Bezafibrate is categorized as a "drug to avoid" mainly because of unproven cardiovascular benefits and increased cutaneous, hematological and renal side effects. [20] This is also consistent with Improving Medicines and Polypharmacy Appropriateness Clinical Tool (IMPACT) that labels Bezafibrate with a limited benefit and rises the ongoing question if adverse reactions outweigh the possible benefits along with close monitoring of renal function and creatinine phosphokinase levels. [21]

Another factor for encouraging deprescribing in our corhort reviewed is the mean TG level which was 197.40 mg/dL that can be reduced by low fat diet along with intensifying statins therapy if needed while addressing patients response according to recent guidelines. In addition, because most of our patients in the reviewed medical records were elderly and diabetic, we inferred no benefit in Bezafibrate treatment based upon subgroup analysis of the FIELD study [22].

On the other hand, Bezafibrate shows benefit as an off-label use in most countries for primary biliary cholangitis. [7] Three patients from out cohort were prescribed for this indication. Two of them had normal TG level and one diagnosed with mild hypertriglyceridemia. It is suggested that Bezafibrate has anti-inflammatory, anti-fibrotic and anti-cholestatic effects, which can be expressed by lowering cytotoxic bile acids within hepatocytes and affecting the cytochrome P450 system [23]. Also, it is expected to lower bilirubin, aspartate aminotransferase, gamma-glutamyl transferase and albumin levels as suggested by Agrawal, et al. [24-25] and resolve symptoms related such as pruritus.

Indeed, these were the three cases in our cohort and intervention by a clinical pharmacist to withhold the treatment was groundless. Instead, a follow up for efficacy was made particularly because the treatment initiated in hospitalization.

We are aware to the fact that we didn't took other risk factors such as obesity and alcohol consumption in consideration to support our intervention because the main focus was the appropriateness of Bezafibrate prescribing based on recent guidelines and current renal conditions.

Gladly, we achieved full collaboration from resident and senior physicians as all inappropriately and contraindicated Bezafibrate prescribing stopped, emphasizing the significant role of a clinical pharmacist as part of a multidisciplinary medical staff along with increasing awareness for this issue. To our knowledge, this is the first report of a real time clinical pharmacist intervention during hospitalization in various hospital departments focusing on appropriateness of Bezafibrate prescribing.

Conclusion

Because most Bezafibrate-treated patients tend to be polypharmic and with other comorbidities, it is obligatory to prescribe it appropriately based on recent guidelines. Efficacy, safety and necessity of Bezafibrate should be evaluated and questioned regularly by prescribers together with renal function follow up and addressing conspicuous side effects, especially when TG level drops below 500 mg/dL or 5.65 mmol/L.

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