Emerging threat of invasive fungal infections

Introduction

Emerging threat of Invasive Fungal Infections

Invasive fungal infection continues to be a major problem associated with high morbidity and mortality mainly to immunocompromised patients as well as to immunocomptent patients but to a much lower extent. (1) Invasive fungal infection and fungemia are caused by a variety of fungal pathogens. The most commonly isolated yeasts are Candida species (spp.) and Cryptococcus spp. Aspergillus species remains the most common mould however, Fusarium spp., Scedosporium spp., Penicillium spp. and Zygomycetes are increasingly isolated.(2) Patients mostly become colonized during hospitalization however, very few patients who become colonized develop sever infection. Nosocomial fungal infections can represent up to 15% of all nosocomial infections.(3) The spectrum of opportunistic invasive fungal infections has increased substantially owing to the rapidly growing population of immunocompromised patients.(4) Due to lack of specificity of symptoms diagnosis of fungal infections can be challenging.(3)

Candida infections are mostly prevalent in critically ill patients in intensive care units (ICUs) and very low birth weight infants. Candidaemia is highly fatal with a reported mortality in the range from 36% to 63%.(5) In the recent years, mortality rates in ICU patients have decreased substantially probably due to earlier initiation of antifungal therapy.(6) Conversely, aspergillosis is the most common fungal infection in immunocompromised most specifically in haematological malignancy and haematopoietic stem cell transplantation (HSCT) patients. Incidence of aspergillosis has increased

considerably but mortality has decreased owing to better diagnosis and treatment.(7)

Treatment of Invasive Fungal Infections

Treatment and prophylaxis of invasive fungal infections involves systemic antifungal therapy. Historically amphotericin B and Flucytosine have been the only available antifungals; these were followed by the development of the older triazole antifungals; fluconazole and itraconazole in the late 1980s. More recent advances have led to the release of amphotericin lipid formulas, newer broad spectrum triazoles (voriconazole, posaconazole) and the newest class of echinocandins.(8)

Amphotericin B either as a deoxycholate or in lipid formulations has been the backbone of antifungal therapy for many years. The triazole antifungals have also emerged as front-line treatment and prophylaxis for many systemic fungal infections. Triazole antifungals used systemically include fluconazole, itraconazole, posaconazole and voriconazole. Fluconazole has a major role in prophylaxis and treatment of both invasive and superficial fungal infection. Voriconazole is the drug of choice in invasive aspergillosis of the lung. Posaconazole is used as a salvage therapy for invasive aspergillosis as well as a prophylaxis in HSCT and neutropenic patients.(9) Itraconazole is active against most fungi except for Zygomycetes.(10) Terbinafine which is widely used in skin infections is also effective against systemic candidiasis including vulvovaginal candidiasis although less effective than fluconazole and itraconazole.(11, 12) Flucytosine is used in combination with amphotericin B

for treatment of severe systemic mycoses and has also in combination with other antifungals for treatment of colorectal carcinoma.(13)

Echinocandins Introduced

Despite the advantages in medical practice and introduction of newer agents, mortality due to fungal infections remained high with mortality due to Aspergillus approaching 100% in HSCT patients.(14, 15) There has also been a change in epidemiology of fungal infections with non-albicans species reaching up to 50% with no significant change in mortality in spite of these newer agents in two studies conducted 15 years apart.(16, 17)

Echinocandins is a newer class of systemic antifungals introduced after almost 15 years of no new agents. They work by inhibiting β-D glucan in fungal cell wall. Echinocandins have favourable kinetics which allows their once daily dosing. (18) The first echinocandin product to be licensed is caspofungin (FDA approved in 2001), that was followed by micafungin (FDA approved in 2005), and anidulafungin (FDA approved in 2006). (19)The discovery of the echinocandin antifungals has provided a new alternative for patients with equal if not higher efficacy relative to older agents and apparently lower toxicity.(20, 21) Echinocandins are extensively used in the treatment of invasive fungal infections mainly invasive candidiasis in neutropenic and critically ill patients.(22)They are also approved as a salvage treatment for invasive aspergillosis.(23) The major advantage of the echinocandins members is their higher efficacy against many candida species including C. glabrata and C. krusei resistant to fluconazole added to their lower toxicity rates compared to older antifungals.(20, 21, 24) The

Infectious Diseases Society of America (IDSA) recommends echinocandins as first line treatment of Candidaemia while caspofungin is offered as an alternative to voriconazole for treatment of invasive aspergillosis.(22, 23) Echinocandins showed equal efficacy to triazole antifungals and even superior efficacy in subgroup analysis since it demonstrates superior efficacy for prophylaxis in patients with hematologic malignancies and undergoing HSCT.(25)

Echinocandins Safety

Treatment of fungal infections is challenging and riddled with adverse events. (26, 27) Echinocandins showed no difference in drug related adverse events and all-cause mortality as compared to triazole antifungals where both groups have shown to be generally well tolerated, nevertheless, echinocandins has significantly decreased adverse event related mortality compared to triazole antifungals.(25) Echinocandins have revealed hepatic toxicity in clinical trials yet the incidence is considered low.(28) The most commonly reported toxicities associated with echinocandins in clinical trials are rash, phlebitis, and nausea. The renal profile of this class appears to be superior to that of older agents.(29, 30) Serious adverse events reported with echinocandins in the context of clinical trials are very few with atrial fibrillation and seizures in two cases treated with anidulafungin and disseminated intravascular coagulation in another one treated with micafungin.(31, 32)

Unfortunately, till now there is insufficient data on the frequency of hepatic and renal toxicities in normal clinical settings although they have already

been reported in context of clinical trials. Moreover, as these agents became more widely used outside clinical trials, new adverse reactions are surfacing. Anidulafungin has been reported to be associated with alopecia in a female patient after several months of treatment.(33) Anidulafungin has also been associated with life-threatening haemodynamic stability in another patient during administration.(34) Three cases has shown a considerable drop in their cardiac index or a worsening of the mean arterial pressure, one following caspofungin administration and the other two post anidulafungin administration.(35) Echinocandins has also been associated with a decrease in cardiac contractility in few case reports and in vitro studies which warrant further investigations.(36, 37) Further studies seem to be mandatory to investigate this potential risk.

Limitations on Detecting Risk

Pre-marketing studies are incapable of detecting rare events. In addition due to their short duration they are also unable to detect delayed toxicities. It's worth noting that to detect doubling of a 0. 1% event with 80% power; more than 50, 000 subjects need to be studied. This leads to drugs being authorized without serious rare events are adequately studied. One cannot also be sure that the safety profile demonstrated in the pre-marketing clinical trials with limited number of subjects remains unchanged when used by millions of patients in normal settings. This difference in safety profile demonstrated is not only attributed to difference in number of users but may also be due to choosing of healthier subjects to participate in clinical trials, providing better care to clinical trials participants in addition to shorter duration of exposure in clinical trials as compared to normal settings. This

difference in safety profile may as well be attributed to the fact that participants in clinical trials are rarely representative to the general patient population. (38, 39)

Post Marketing Risk Detection

Pharmacovigilance is defined as the continuous process of detecting, evaluating, communicating and improving safety of medicines under normal conditions.(40) Post marketing data on adverse events include spontaneous case reports, medical record databases, and data collected in prospective postmarketing studies.(41) Spontaneous reports are unsolicited reports of clinical observations originating outside of a formal clinical trial and that are submitted to regulatory agencies or drug manufacturers.(42) The report is considered important if it involves an ADR that is new, rare, serious or occurring at a higher frequency than expected.(43)

Spontaneous reporting systems have a potential for detecting or ' signalling' new ADRS that have not been previously recognized in clinical trials.(38) The most crucial factor that determines the value of spontaneous reports is the quality of submitted reports and whether it has a complete description of the ADR, patient demographics, baseline characteristics other confounding factors or medication and temporal relation.(42) Signal detection using large postmarketing ADRs databases is the first step in detecting unknown and unexpected associations between drug exposure and adverse events which has to be followed by qualitative case-by-case analysis to identify signals that may be of value or warrant further investigation.(44, 45) Safety

evaluators usually look at common trends or patterns or and potential causal relations. (42)

Advantages and Limitations of Spontaneous Reporting

In all countries, the nation pharmacovigilance system relies on spontaneous reporting by healthcare practitioners, patients and manufacturers to the national coordinating center.(46) Spontaneous reporting is the only source of pharmacovigilance that provides the highest volume of data at the lowest cost.(47) The most important function of spontaneous reporting is early detection of signals which helps in hypothesis formulation that may lead to initiation of confirmatory investigations or regulatory actions that may end up with warnings, label changes or product withdrawal.(48, 49) Large postmarketing databases are the most important source for mining of drug safety data, however, analysing data from these databases is very challenging owing to the limitations of these unsolicited reporting systems. (50)

One of the most important limitations of spontaneous reporting is the quality of data since cases are mostly poorly documented with no follow up data which necessitates contacting the reporter for more data.(42) Another limitation is under-reporting whose extent is very hard to estimate and which depends on many factors including the severity of the reported ADR among many other factors.(51, 52) Reporting rate also undergoes fluctuation along the drug life cycle with higher rates noticed when the drug is newly introduced to the market (weber effect). Higher reporting rates are also noticed for serious medical events or after negative publicity. (53) It's

estimated that FDA receives only 1% of ADRs in one study and 8% in another of all occurring ADRs which affects is reflected on the inability of spontaneous reporting system to estimate incidence of a specified ADR. (54, 55)

Role of Data mining in Pharmacovigilance

The role of data mining in the field of pharmacovigilance is evolving. At the outset, it's worth noting that data mining methods involve identifying the observed relation between a drug and a certain ADR. These relation identification methods are based totally on the frequency with which the drug and event are reported. The relations identified using these data mining techniques cannot be used to prove or negate a causal relation.(50)

Data mining methods can elucidate complex drug issues such as concomitant medications or conditions that may not be investigated using traditional methods. However, this is usually confronted by the non-systematic attainment of background rates of adverse events and drug exposure data which hinder estimation of risk based on spontaneous reporting databases.(56, 57)

In the context of data mining, the term ' signal' is used to refer to a quantitative association between a drug and an event which exceeds a certain threshold set by the investigator that warrant further evaluation. The ' signal score' is the number reflecting the strength of the quantitative association which reflects how much the observed frequency differs from that expected.(50, 56, 58) The application of computational and statistical methods to large drug safety databases for identifying drug-event pairs

disproportionately reported at higher frequency than expected by a statistical independence model is referred to as ' Safety data mining' and ' disproportionality analysis'.

Many data-mining methods are applied to pharmacovigilance; the ones that are most commonly reported in the literature are the proportional reporting ratio (PRR) and the reporting odds ratio (ROR) in addition to the Bayesian and empirical Bayesian methods.(59–62)

Signal Detection Methods

Disproportionality analysis is the main concept behind computerized pharmacovigilance methods. Disproportionality analysis is dependent on the construction of a 2×2 contingency table as shown in table (1). (63) Disproportionality methods differ in how they are calculated and how they account for low counts. They are generally classified into Frequentist and Bayesian approaches.

Drug of interestOther drugs

Event of interestab

Other event cd

Table 1: Statistical significance in spontaneous reporting is calculated using the frequencies in the table above

Frequentist approaches

Frequentist approach usually accompanied by hypothesis testing of independence using chi-square or Fisher's exact test.(64)

Proportional reporting rate (PRR) or Case/Non-case design

PRR can be considered as an approximation of conditional probability and is calculated using the following equation: PRR= = a/(a+c) ÷ b/(b+d). Where a/(a+c) can be perceived as the probability of developing the event of interest given that the drug of interest is taken and an event in turn, b/(b+d) can also be perceived as the probability of developing the event of interest given that another drug is received given that any other drug is taken and an event occurred.(63) PRR is a valuable aid to signal generation which is easy to calculate and interpret with various refinements made possible.(59)

Reporting Odds Ratio

ROR is a ratio of two ratios and is calculated according to the equation: ROR= a/b÷c/d where a/b is the ratio of the patients who had the event of interest a divided by the number of patients who had the event while taking other medications. This ratio in turn is divided by c/d which is calculated by dividing all patients who had the drug of interest but did not have the event of interest by all other patients who did not have the event of interest given that they took any other drugs. (63) ROR is not affected by general under reporting for a specific drug or as specific event.(65) It has been proposed that ROR may be less biased than other disproportionality methods being considered as the case-control studies analysis.(66) Nevertheless, others believe that in practice there is no difference in performance between ROR and PRR.(60, 67)

Bayesian approaches

Bayesian approaches tries to account for uncertainty in disproportionality measure calculated from small samples by shrinking the disproportionality measure towards baseline case of no association. This shrinking is a reduction of spurious associations when there are not enough data to support it and is proportional to the variability in the disproportionality statistics.(64)

The Bayesian approaches include Multi-item Gamma Poisson Shrinker (MGPS) which is currently used by the FDA.(68, 69) MGPS is based on an empirical Bayes framework and its computed measure is called empirical Bayes geometric mean (EBGM) which is the Bayesian version of the Relative Reporting Ratio (RRR). RRR is the ratio of the incidence of the observed incidence rate of a drug-event pair to its expected rate under the assumption that the drug and event are independent.(70)

Another Bayesian approach adopted by the WHO is called Bayesian Confidence Propagation Neural Network (BCPNN), which estimates a Bayesian version of the Information Component (IC). A positive IC indicates that based on all reports in the database the drug-event pair is reported more often than expected. (61)

Postmarketing Safety Databases for Signal Detection

Databases utilized in drug safety data mining are postmarketing databases maintained by manufactures, regulators and different consortia. These databases are different in their reporting guidelines, coding dictionaries and

rules for data entry. These databases vary in size and may reach millions of reports. The analysis of these databases may yield different results and so a single database available to all stakeholders is needed. Ideally this database will not have duplicate reports or missing data and is consistently coded for drug and event name.

A number of databases are commonly available for signal detection activities, however; they differ in accessibility. These include the database of the WHO International Drug Monitoring Programme and the FDA's public release safety database (AERS).(50)

WHO Safety Database

The WHO safety database is a large database receiving AEs from the national collaborating centers participating in the WHO Drug monitoring program.(71) It has the advantage of having the drug names coded according to the Anatomical Therapeutic Chemical (ATC) classification and ADRS are coded using the WHO Adverse Reaction Terminology. However, data is accessible by subscription only.(68)

European Medicines Agency EudraVigilance database

The EMEA pharmacovigilance system is called the EudraVigilance. It has 2 modules one for clinical trials and another for post marketing surveillance. It has analytical capabilities and performs signal detection in terms of PRR and ROR. It has restricted access even to manufacturers who can only see reports that they have submitted to the EMEA.(72)

US FDA Adverse Event Reporting System (AERS)

AERS is the FDA's postmarketing safety database. AERS database is intended to support the FDA's post-marketing safety surveillance program for drugs. It relies on unsolicited reports submitted by healthcare professionals and patients on adverse events and medication error reports as well as required reports by manufacturers and so represents a useful resource for investigating drug safety.(73) The public-release version of AERS is available beginning with January 2004 as quarterly data directly downloadable from the FDA website. The new FDA FAERS was launched in the 10th September, 2012, and replaced the Adverse Event Reporting System (also known as Legacy AERS).(74)

The main aim of the current study is to:

Map the safety profile of echinocandins antifungals. as compared to other drugs.

Compare the safety profile of echinocandins to that of other systemic antifungals.

Assess the effect of changing the reference group on the top signals identified.

To achieve these aims data mining methods and disproportionality analysis will be employed to the FDA AERS to achieve these aims. This study will therefore add to the knowledge on the safety profile of this newer class of antifungals.