Drug Information Bulletin

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Content

Editorial

Presently 179 Adverse Drug Monitoring Centers (AMC) are collecting ADR data regularly and collected about 1.4 lacks of ADR under the Pharmacovigilance Programme of India (PvPI). PvPI is now contributing considerable amount of ADR data to the Uppsala Monitoring Centers (UMC)- a WHO collaborating centre.

3rd version of Pharmacovigilance system in India started in the year of 2010 operating from Indian Pharmacopoeia Commission (IPC) and growing with a steady pace. In order to collect the data from specialized areas two more wings have been developed, which are Haemovigilance Programme (HvPI) and Materiovigilance Programme (MvPI). Haemovigilance Programme (MvPI) started since 10th Dec. 2012 in collaboration with National Institute of Biologicals (NIB) and Materiovigilance programme started since 6th July 2015, Indian Pharmacopoeia Commission (IPC) as National Coordinating Centre & Sree Chitra Tirunal Institute of Medical Sciences & Technology (SCTIMST) will be function as National Collaborating Centre.

Now Adverse Events Following Immunization (AEFI) is also integrated with PvPI. PvPI, CDSCO and Pharmaceutical Industries working to Harmonize PSUR reporting.

AMCs have also started in focused therapeutic areas like Anti-tubercular drugs. ADRs are being collected from six centers spread over the country on newly introduced anti-tubercular Drug- Bedaquiline.

PvPI is also collaborating with Medical Council of India (MCI), Indian Medical Association (IMA) and some other organizations for more intensive Pharmacovigilance. It is felt by the experts that the system is working well and will serve the society continuously.

Dr. Subhash C. Mandal
Editor

New Drug: Nintedanib

Approved indication: idiopathic pulmonary fibrosis, non-small cell lung cancer

Ofev 100 mg and 150 mg capsules

Australian Medicines Handbook section 14.2.3

Growth factors contribute to the proliferation of cells in cancers and conditions such as pulmonary fibrosis. This proliferation involves tyrosine kinases such as fibroblast growth factor, vascular endothelial growth factor and platelet-derived growth factor. Nintedanib inhibits these growth factors by binding to their receptors intracellularly. This disrupts the signalling needed for cell proliferation.

Nintedanib capsules are taken twice daily with food. There is extensive first-pass metabolism so the bioavailability is under 5%. The drug is also mainly cleared by metabolism with most of the metabolites being excreted in the faeces. The terminal half-life is 10–15 hours. As nintedanib is a substrate of P-glycoprotein, inducers of this transporter, such as phenytoin and St John's wort, will reduce the concentration of nintedanib. Its plasma concentration will be increased by inhibitors of P-glycoprotein such as ketoconazole.

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis is one of the interstitial lung diseases. A proliferation of fibroblasts leads to progressive breathlessness. The median survival is 3–5 years.

The main clinical trials of nintedanib in pulmonary fibrosis were INPULSIS-1 and -2.[1] In these trials a total of 638 patients were randomised to take 150 mg nintedanib twice daily for 52 weeks and 423 were given a placebo. These patients all had a forced vital capacity (FVC) that was at least 50% of the predicted value. In INPULSIS-1 the FVC fell by 239.9 mL/year with placebo and by 114.7 mL/year with nintedanib. The respective figures in INPULSIS-2 were reductions of 207.3 mL/year and 113.6 mL/year. The smaller decline in lung function with nintedanib was statistically significant.

In INPULSIS-1, 21% of the patients had to discontinue nintedanib because of adverse events. In both trials more than 60% of the patients taking nintedanib developed diarrhoea compared with about 18% of the placebo group. Other adverse events that were more common with nintedanib than with placebo included nausea, vomiting, weight loss and elevated liver enzymes.[1]

Lung cancer

The inhibition of growth factors by nintedanib has been studied in patients with non-small cell lung cancer of different histological types. The LUME-Lung 1 trial involved 1314 patients with locally advanced, metastatic or recurrent disease that had not responded to first-line chemotherapy. All the patients were given an infusion of docetaxel every 21 days and 652 also took 200 mg nintedanib twice daily on days 2–21 of the cycle. The median duration of treatment was 2.8 months with docetaxel alone and 3.4 months with the combination. After a median follow-up of 7.1 months, progression-free survival was 2.7 months in the control group and 3.4 months in the combination group. This difference is statistically significant.[2]

Adverse events led to 21.7% of the patients taking docetaxel and 22.7% of those taking docetaxel and nintedanib withdrawing from the trial. Deaths from adverse events were more frequent with the combination treatment. Nausea, vomiting, diarrhoea, altered liver function and febrile neutropenia were also more frequent.[2]

Precautions

The adverse effects of nintedanib may require treatment to be interrupted or reduced. Blood counts and liver function should be regularly monitored. Nintedanib is not recommended for patients with moderate or severe liver disease. In addition to the common adverse effects, there may also be an increased risk of gastrointestinal perforation, impaired wound healing, bleeding and thromboembolism. Although patients with a history of myocardial infarction or stroke were excluded from the INPULSIS trials, myocardial infarctions were more frequent with nintedanib than placebo (1.6 vs 0.5%).

Conclusion

Idiopathic pulmonary fibrosis has a poor prognosis, so reducing the decline in lung function is a benefit. However, in a pooled analysis of the INPULSIS trials, nintedanib had no significant advantage over placebo in preventing acute exacerbations in pulmonary fibrosis or in health-related quality of life.[1]

In non-small cell lung cancer adding nintedanib to docetaxel increases

progression-free survival, but the median overall survival is not significantly increased unless the cancer is an adenocarcinoma. The median overall survival for patients with an adenocarcinoma given the combination was 12.6 months compared with 10.3 months for patients treated with docetaxel alone. Pemetrexed is another drug that can be used to treat non-small cell lung cancer. In March 2015 the Pharmaceutical Benefits Advisory Committee concluded that an indirect comparison did not show that the effectiveness of nintedanib and docetaxel was non-inferior to pemetrexed.3

References:

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Import of Medical Devices and Implants

cardiovascular morbidity and mortality with rheumatic heart disease being the dominant Valvular Heart Disease (VHD) in developing countries including India. Indian Council of Medical Research (ICMR) has informed that as per experts, around 15-20% of total patients attending the hospitals with heart disease suffer from VHD.

A position paper published by Federation of Indian Chambers of Commerce & Industry (FICCI) (2014-15) informs that Indian medical device industry is primarily import driven with imports contributing close to 75% of the market. Medical electronics and Hospital equipments and surgical instruments form more than 50% of sale with 87% being imported as per the document on "Recommendations of Task Force on the Medical Devices sector in India - 2015".

As informed by Department of Pharmaceuticals, the Government of India had taken up the issue with leading manufacturer of stents to reduce the prices voluntarily. As an outcome one manufacturer has reduced the prices of coronary stents by 10%. Further, a few other manufacturers have informed that there has been substantive reduction in prices of coronary stents manufactured by them.

As informed by Drug Controller General of India, the Drugs & Cosmetics Act and Rules there under do not mandate that maximum retail price (MRP) should be indicated on the label.

The Health Minister, Shri J P Nadda stated this in a written reply in the Lok Sabha here today.

Ayush medicines quality: States asked to equip themselves

With concerns being expressed over standard of Ayush medicines, the Centre today asked states to equip their regulatory framework and infrastructure to meet the quality requirements prescribed by law.

"We are very much concerned about the weak control and sale of sub-standard and spurious Ayush medicines. In every Parliament session, we get a lot of questions on sub-standard drugs and quality," Union Minister of State for AYUSH, Shripad Naik said.

Particularly, complaints about misleading advertisements and tall claims of Ayush medicines have been brought to "our notice by Ministries of Consumer Affairs and Information and Broadcasting and Drug Controller General," he said addressing a conference on Ayush here.

"Quality control of Ayush drugs is statutory requirement in accordance to the quality requirement in provisions of Drug and Cognitive Act. Unfortunately, on this front, focussed efforts have not been made in the enforcement mechanism by states to ensure manufacturing and sale of quality-assured medicines," he said.

The Ayush Minister rued that several states do not send Action Taken Report despite several advisories and directives.

"I call upon all state authorities to equip their regulatory framework and add up their infrastructure facilities and technical manpower," Naik said.

Noting that there are several financial constraints being faced by the states in building up infrastructure, he suggested that they can avail funds under National Ayush Mission for the facilities.

Tramadol: Risk of slowed or difficult breathing in children in USA

The US FDA has been investigating the use of tramadol in children aged 17 years and younger, for risk of slowed or difficult breathing. This risk may be increased in children treated with tramadol for pain after surgery to remove their tonsils and/or adenoids. Tramadol is not approved for use in children in USA, however, data show it is being used "off-label" in the paediatric population.

There is a genetic variation in the metabolism of tramadol, and some individuals convert tramadol to the active form of the opioid, called Odesmethyltramadol faster than usual. This can lead to higher blood levels, resulting in breathing difficulties that may lead to death. The FDA has recommended that parents and caregivers of children taking tramadol who notice any signs of slow or shallow breathing, difficult or noisy breathing, confusion, or unusual sleepiness should stop tramadol and seek medical attention immediately by taking their child to the emergency room or calling the ambulance. The FDA is evaluating all available information and will communicate final conclusions and recommendations to the public when the review is complete. Reference: Drug Safety Communication, US FDA, 21 September 2015 (www.fda.gov) (See WHO Pharmaceuticals Newsletter No.5, 2015: Tramadol oral drops not for children under the age of 12 years in Australia)

Roxithromycin: Risk of QT prolongation, ventricular tachycardia (including torsades de pointes) and pseudomembranous colitis found in Japan

MHLW and the PMDA have announced the revision of the package insert for roxithromycin (Rulid®) to include risk of QT prolongation, ventricular tachycardia (including torsades de pointes) and pseudomembranous colitis. Ceftriaxone is an antimicrobial used for treatment of superficial skin infections, deep-seated skin infections, lymphangitis/lymphadenitis, chronic pyoderma by strains of genus Staphylococcus, genus Streptococcus, Pneumococcus, Moraxella (Branhamella) catarrhalis, Propionibacterium acnes, and Mycoplasma pneumoniae. The MHLW/PMDA stated that cases of pseudomembranous colitis, QT prolongation and ventricular tachycardia (including torsades de pointes) have been reported in patients treated with roxithromycin in Japan and in other countries. In addition, the company core datasheet (CCDS) has been updated. Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of "QT prolongation and ventricular tachycardia (including torsades de pointes)" and "Pseudomembranous colitis" to the section of the "Clinically significant adverse reaction" in the package insert. The MHLW/PMDA also recommended the addition of the "Patients with risk of prolonged QT" to the section of the "Careful administration" in the package insert. Reference: Revision of Precautions, MHLW/PMDA, 20 October 2015 (www.pmda.go.jp/english/).

Pictures from the lecture on "Life & works" of Acharya P.C.Ray held on 14th Feb. 2016