Drug Information Bulletin

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Editorial

Death due to Tuberculosis is a global problem and this problem has been aggravated by development of Multidrug Resistant TB (MDR-TB) and Extremely Drug Resistant TB (XDR-TB). In 2014 about 480000 people developed MDR-TB globally and about 9.7% of these cases were XDR-TB.

The Govt. of India started a Revised National Tuberculosis Control Programme in 1997 to eradicate TB. RNTCP followed the WHO recommendation of Directly Observed Short Course (DOTS) strategy and reaches over a billion people in 632 districts. One of the shortfalls of this programme is discontinuation of treatment because of several reasons. Now Govt. of India recognizes services of private facilities, and are also taking help of NGOs to facilitate the RNTCP Programme.

Indian Pharmaceutical Association (IPA) is working for TB Care and Control utilizing the services of the community pharmacists as they are more accessible to the TB patient. In 2011 World Health Organization (WHO) signed a MOU with FIP at Hyderabad during FIP congress in 2011. Thereafter TBC, Govt. of India has signed a MOU with IPA, PCI, SEARPharm Forum & AIOCD for care & control of tuberculosis. As per this agreement IPA has started working in different states involving Pharmacists working in community Pharmacy and have experienced extremely positive outcome.

Recently RNTCP has given direction to all state TB officers to involve community pharmacists in this programme. Along with all other states, State TB officer of West Bengal has given direction to the Chief Municipal Health Officer and CMOH of all districts for involving community Pharmacist in RNTCP for early detection, referral of TB suspects for treatment, DOT provision for TB treatment and generating awareness about TB and MDR-TB.

This is a golden opportunity for the community pharmacists to serve the community and hope they will extend all sorts of help for success of this programme.

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New Drug: Tofacitinib for rheumatoid arthritis

Approved indication: Rheumatoid arthritis
5 mg film-coated tablets
Rheumatoid arthritis is now managed with disease-modifying antirheumatic drugs, such as methotrexate. If there is an inadequate response, a biological drug may be prescribed. These include the tumour necrosis factor (TNF) alpha antagonists, such as adalimumab and etanercept. The choice of treatment for moderate to severe active rheumatoid arthritis has now been expanded with the approval of tofacitinib. This is a Janus kinase inhibitor, which blocks the cytokine pathway that leads to the activation of lymphocytes. The Janus kinase inhibitors therefore have effects on immune and inflammatory processes.1,2

In contrast to adalimumab and etanercept, tofacitinib can be taken orally. Although a steady state is achieved after 24–48 hours of tofacitinib 5 mg twice daily, the maximum effect on lymphocytes takes 8–10 weeks. Most of the drug is metabolised, primarily by cytochrome P450 (CYP) 3A4. Tofacitinib is therefore contraindicated in severe liver disease and can interact with inducers and inhibitors of CYP3A4. As 30% of the drug is excreted unchanged, a dose reduction is recommended if the patient has a creatinine clearance below 50 mL/minute.

The clinical trials of tofacitinib assessed patients using the criteria of the American College of Rheumatology (ACR). The outcomes were measured by the reduction in the number of affected joints and improvements in other assessments. For example an ACR20 response represents a 20% change from baseline.Tofacitinib monotherapy was studied in a trial of 611 patients who had had an inadequate response to a disease-modifying drug. Four different regimens were studied with efficacy assessed after three months. Among the patients taking the recommended dose of 5 mg twice daily, 59.8% achieved an ACR20 response compared with 26.7% of the placebo group. The corresponding results for an ACR70 response were 15.4% versus 5.8%.3

Another trial compared tofacitinib monotherapy with methotrexate in 956 patients who had not previously been treated with methotrexate. After six months 25.5% of the 369 patients who took tofacitinib 5 mg twice daily had achieved an ACR70 response. Only 12% of the 184 patients who took methotrexate achieved this response. X-rays showed significantly less disease progression with tofacitinib.4

Tofacitinib has also been studied in combination with methotrexate or other (non-biological) disease-modifying antirheumatic drugs. Patients who had had an inadequate response to previous treatment either added tofacitinib or a placebo. Most (79%) of the 795 patients were taking methotrexate. At six months an ACR20 response had been achieved by 52.1% of the 315 patients treated with tofacitinib and 30.8% of the 159 patients taking placebo.5

The combination of tofacitinib and methotrexate has been studied in a trial that investigated the radiological changes in the joints of 800 patients. After six months, 51.5% of the 321 patients who took tofacitinib 5 mg twice daily had achieved an ACR20 response compared with 25.3% of the 160 patients in the placebo groups. Compared to methotrexate alone, the combination resulted in less joint space narrowing and fewer erosions on X-ray. However, the 5 mg dose was not statistically superior to placebo at six months.6

For patients with arthritis that is not adequately controlled by methotrexate, adding a TNF antagonist may be considered. This strategy has been

compared to adding tofacitinib in a trial involving 717 patients. There were five different regimens in this trial. Two involved starting patients on placebo before switching to tofacitinib. The comparison regimen was adalimumab injected every two weeks. At six months the ACR20 response was achieved by 51.5% of the patients taking tofacitinib 5 mg twice daily and 47.2% of the patients given adalimumab. This response was only achieved by 28.3% of the patients in the placebo groups.[7]

Tofacitinib has also been studied in patients who have had an inadequate response to TNF antagonists. The four regimens in the trial either added tofacitinib to methotrexate at the start of the study or after three months on placebo. There were 399 patients of whom 133 took tofacitinib 5 mg twice daily for six months. Most of the patients had previously tried adalimumab or etanercept. Three months after adding tofacitinib 5 mg the ACR20 response was 41.7% whereas only 24.4% of the 131 patients in the placebo groups had responded.[8]

As tofacitinib acts on the immune system, patients have a higher risk of serious infections. Hepatitis B and C, and tuberculosis should be excluded before treatment begins. Live vaccines should not be given. Serious infections in the trials included cellulitis, herpes zoster, pneumonia and urinary tract infections. Tofacitinib will reduce neutrophil and lymphocyte counts. Regular monitoring is required as neutropenia and lymphopenia may require treatment to be stopped. The patient's haemoglobin should also be monitored as life-threatening anaemia has been reported.[7]

Routine monitoring of liver function is recommended and the patient's lipid concentrations will also need to be measured as tofacitinib increases cholesterol concentrations. Although the relationship to tofacitinib is unclear, serious adverse events have included gastrointestinal perforation, interstitial lung disease, lymphoma and skin cancer.

Tofacitinib should not be used in pregnancy or lactation, or by women trying to conceive. It does not affect the pharmacokinetics of combined oral contraceptive pills.

While tofacitinib produces a 20% improvement in ACR criteria for some patients, there is less evidence about its effect on the long-term progression of rheumatoid arthritis. The potential advantages of tofacitinib have to be balanced against the risk of possibly fatal adverse reactions. Whether the risk of harm is greater than with other biological drugs is currently unclear. The combination of tofacitinib with other biological or immunosuppressive drugs is contraindicated. Longer term study will be needed to establish the place of tofacitinib in the treatment of rheumatoid arthritis. It will probably be reserved for specialist use in patients with arthritis that has not responded to other disease-modifying drugs.

REFERENCES:

1. Kubler P. Janus kinase inhibitors: Mechanisms of action. Aust Prescr 2014;37:154-7.
2. Walker J, Smith M. Janus kinase inhibitors in rheumatoid arthritis: Clinical applications. Aust Prescr 2014;37:158-60.
3. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al.; ORAL Solo Investigators. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012; 367:495-507.
4. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al.; ORAL Start Investigators. Tofacitinib versus methotrexate in

rheumatoid arthritis. N Engl J Med 2014;370:2377-86.
5. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med 2013;159:253-61.
6. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al.; ORAL Scan Investigators. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum 2013;65:559-70.
7. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, et al.; ORAL Standard Investigators. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367:508-19.
8. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al.; ORAL Step investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet 2013;381:451-60.

Ref.: Aust Prescr 2015; 38:217-25

Status in India: *Tofacitinib Tablets 5 mg approved by DCGI on 01.04.2016 "For the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to Methotrexate. It may be used as monotherapy or in combination with Methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs)".*

Ref. www.cdsco.nic.in

Tramadol oral drops not for children under the age of 12 years

The TGA has reminded health-care professionals that tramadol oral drops (Tramal®) are not approved for use in children under the age of 12 years and no dosing instructions are provided for this age group in the Product Information. Tramadol is a centrally-acting synthetic analgesic of the aminocyclohexanol group with opioid-like effects. The reminder follows the death of a two-year-old Australian child as a result of tramadol toxicity following treatment with tramadol oral drops. The TGA has provided the following information for health-care professionals: • Tramadol oral drops are safe and appropriate for use in adult and adolescent patients for whom the medicine is approved, however, given the concentration of the drops (100 mg/mL), there is a potential risk of overdose in children. • The dosing recommendations in the Product Information for tramadol oral drops are only valid for adults and adolescents over the age of 12 years. • Use of tramadol oral drops in children under the age of 12 years is off-label. • This medicine should only be prescribed for patients in the approved age group.
Reference: Medicines Safety Update, TGA, Vol. 6, No. 4, August 2015 (www.tga.gov.au)

USFDA releases guidance on osteoporosis treatments

New draft guidance urging osteoporosis drugmakers to conduct long-term nonclinical bone quality studies has been issued by the FDA to determine the effects of long-term use of osteoporosis treatments on patients' bone quality. The agency said the studies must be nonclinical, because "there are no validated and reliable methods for the noninvasive assessment of bone quality in humans." Ref.: Regulatory Focus

NICE criticized by charity group over breast cancer drug

Breast Cancer Now, a UK-based breast cancer charity, called for women in the UK to get access to Pfizer's breast cancer treatment Ibrance, or palbociclib, which is already approved in the US but not yet available in Europe. The charity said the National Institute for Health and Care Excellence has not approved breast cancer drugs for the past seven years and is worried that the drug will be judged as not cost-effective by NICE's appraisal system.

Ref.: The Guardian (London)

India mandates lower prices for several cancer drugs

India's National Pharmaceutical Pricing Authority has cut the prices of 56 drugs designated as essential medicines, including imatinib, which is used to treat blood and stomach cancers. The authority also capped the retail price of the injectable metastatic breast cancer drug paclitaxel.

Ref.: The Economic Times (India)

EU wants FDA and EMA to synchronize rules

The European Union proposed synchronizing the FDA's and the European Medicines Agency's drug approvals, guidelines and good manufacturing practice compliance rules to remove duplicate GMP inspection and clinical trial requirements. Discussion of the proposal will take place at the Transatlantic Trade and Investment Partnership discussions.

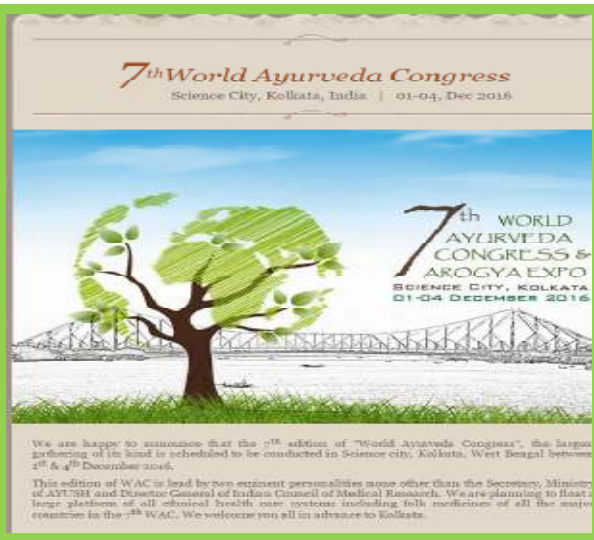
Ref.: FDAnews

FDA simplifies guidelines on investigational drug access

Two guidance documents on expanded access to investigational drugs for patients with life-threatening conditions and charging for investigational drugs, plus a new form to request expanded access called Form FDA 3926, were finalized by the FDA. The revised question-and-answer guidance documents and the new form provide clarification and are based on public comment, the agency said.

Ref.: Regulatory Focus

Forthcoming Events:



and

Ethnopharmacology Conclave

3rd – 4th Dec 2016

Title: "INTERNATIONAL CONCLAVE ON ETHNO-MEDICINE ETHNOPHARMACOLOGY AND TRADITIONAL HEALTH PRACTICES"

"Learning from the Nature : Tradition to Innovation".

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