AUGUST 2012 / VOLUME 2 / ISSUE 2

BULLETIN ON ADVERSE DRUG REACTIONS

LOKMANYA TILAK MUNICIPAL MEDICAL COLLEGE & GENERAL HOSPITAL

Department of Pharmacology

LTMMC & LTMGH, Sion, Mumbai - 22

Committee Members for Bulletin on Adverse Drug Reactions

Lokmanya Tilak Municipal Medical College & General Hospital, Mumbai

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From the Editor's Desk

Dear Friends and Colleagues,

It gives me great pleasure to present to you yet another issue of Bulletin on Adverse Drug Reactions.

We are aware that pharmacovigilance is also applicable to vaccines in addition to drugs. The issues related to pharmacovigilance are however little different for vaccines compared to conventional drugs. The article on the Pharmacovigilance of Vaccines will give you an overveiw on various aspects of adverse effects of vaccines, their differences with the adverse effects of conventional drugs and their surveillance.

Other features in this issue include a case study on psoriasis emphasising the importance of patient monitoring for the prevention of untoward effects and a review article on Drug Hypersensitivity.

I hope the readers find the articles interesting and informative.

Finally, I would like to thank all the clinical departments for continuing and increasing their valued support in ADR reporting and also to all the members of Department of Pharmacology for their efforts in bringing out current issue of the bulletin.

Thank you

Dr Sudhir Pawar

DRUG HYPERSENSITIVITY

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Introduction

Drug hypersensitivity reactions (HSR) are the adverse effects of drugs which clinically resemble allergy and occur at doses generally tolerated by normal subjects. Although they occur in a small percentage of patients, these reactions are often unpredictable and can be life threatening. Drug hypersensitivity reactions comprise of allergic and pseudo-allergic reactions. Allergic reactions have well defined immunological mechanism and may present as cutaneous reactions or systemic reactions with major organ involvement or both. These reactions can manifest either as immediate IgE mediated reactions (occurring in less than 1 hour after the last drug intake e.g. urticaria, angioedema and anaphylaxis) or delayed non-IgE mediated reactions (occurring beyond an hour and up to several days after the last drug intake e.g. maculopapular eruptions, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome). Incidence of HSRs is reported to be high with penicillin, anticonvulsants, NSAIDs and anti-malignancy drugs.[1] Pseudoallergic (anaphylactoid) reactions are immediate systemic reactions that mimic anaphylaxis but are caused by non-IgE-mediated release of mediators from mast cells and basophils and do not require a preceding period of sensitization. Drugs known to cause pseudoallergy include (Radio) contrast media, neuro-muscular blockers, plasma expanders, acetylsalicylic acid, diclofenac, mefenamic acid, ibuprofen, vancomycin, quinolones, etc.[1,2,3]

Unpredictable nature of these reactions and also the difficulty in assessing the severity of the onset of reactions often leads to discontinuation of useful drugs. On the other hand knowledge of susceptibility of a patient to develop HSR to a particular agent might reduce morbidity and mortality. Hence an understanding of HSR along with its immunological mechanisms and clinical management of the same is important for all clinicians.

Mechanism Of Drug Allergy

There are three main mechanisms by which the drugs can stimulate the immune system:

Hapten concept: Drugs are foreign particles and hence capable of eliciting antigenic reactions. Small chemical compounds, usually less than 1000 Da, are not immunogenic per se. However, if the chemical is reactive and able to bind covalently to proteins (soluble e.g. albumin or cell-bound e.g. an integrin), DNA, etc., a new antigenic determinant called hapten arises that can produce a new immune response. Drugs/haptens bind covalently to and activate IgE or IgG,

leading to reactions like anaphylaxis, haemolytic anemia and thrombocytopenia. Haptens can also bind directly to the immunogenic major histocompatibility complex (MHC)/peptide complex on antigen-presenting cells (APC) activating T-cell reactions with exanthem, hepatitis, interstitial lung disease, contact dermatitis, etc.[4,5]

Prohapten concept: Some drugs are prohaptens, requiring metabolic activation to become haptens. The metabolism leads to the formation of a chemically reactive compound (e.g. from sulfamethoxazole [SMX] to the chemically reactive form sulfamethoxazole nitroso [SMX-NO]) similar to a hapten.

p-i concept: Drugs are often designed to fit into certain proteins/enzymes to block their function. Some drugs may also bind by reversible van der Waals bond to some of the available T-cell receptors (TCR) or major histocompatibility complex (MHC) molecules and lead to an immune response. This has given rise to p-i concept i.e. pharmacologic interaction with immune receptors. This results in an exclusive T-cells stimulation and subsequent infiltration of the skin, other organs resulting in a T-cell mediated inflammation. The p-i concept suggests that certain drug hypersensitivities are pharmacologic reactions, because the drug interacts not only with the target for which it is designed but also with some immune receptors. Because of this p-i concept, many of the unpredictable type B drug reactions may become predictable drug reactions and might help for personalized medicine.[4,5]

The following table gives a summary of various types of Drug Hypersensitivity Reactions, their mechanisms, causative agents and diagnostic tests.

Table 1: Summary of Drug Hypersensitivity Reactions[2,4,6]

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IFNγ/TNFα (TH1 cells)	IL-5,IL-4/IL-13(TH2 cells)	Perforin/ Granzyme B (cytotoxic T-cell Lymphocytes)	CXCL, GM-CSF (T-cells)
Antigen	Soluble antigen	Cell or matrix associated antigen	Soluble antigen	Antigen presented by cells or direct T-cell stimulation	Antigen presented by cells or direct T-cell stimulation	Cell associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T-cell stimulation
Effectors	Mast cell activation	Phagocytes, NK cells	Comple-ments, neutrophils	Macrophage activation	Eosinophils	T-cells	Neutrophils
Examples of hypersensitiv-ity reactions	Systemic anaphylaxis, asthma, allergic rhinitis	Haemolytic anemia, Neutropenia, Thrombocy-topenia	Serum sickness, Arthus reaction	Tuberculin reaction, contact dermatitis	Chronic asthma, chronic allergic rhinitis, maculopapu-lar exanthema with eosinophilia	Contact dermatitis, maculopapular and bullous exan-thema, hepatitis	Acute generalized exanthema-tous pustulosis, Behcet's disease (immune vasculitis)

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Causative drugs	β-lactams, neuromuscular blocking agents, quinolones	Penicillin, sulphonamides	Phenytoin, salicylates, barbiturates, NSAIDs, isoniazid, antisera, hydralazine, captopril, sulfonamides, procainamide induced lupus	Sulfonamides, β-lactams			
Timing of reactions	Minutes-hours after drug exposure	Variable	1-3 weeks after drug exposure	2-7 days after drug exposure			
Diagnostic work up	Specific Ig E levels, Skin testing for antigen-specific IgE, mast cell activation, serum histamine & tryptase levels, in vitro drug test for allergy	Complete blood count, direct and/or indirect coomb's test	ESR, CRP, test for complement levels (C3, C4, CH50), autoantibody test (anti-nuclear antibody, anti- histone antibody)	Patch testing for specific drugs			

Patients At Risk For Drug Hypersensitivity Reactions:

Some patients have an increased risk of developing a drug-hypersensitivity reaction, e.g. those with history of prior drug reactions, concomitant illnesses (viral infections, auto-immune reactions, blood cell malignancies). These patients need to be identified early and in some cases precautions may be taken. Certain drug related factors like multiple drug therapy, repeated administration of same drug, topical route of drug administration and elevation of drug dose in chronic therapy may increase the likelihood of a patient developing hypersensitivity reactions. Immunogenetic factors can also play a role in development of HSR. Certain HLA-B alleles predispose for drug allergies e.g. abacavir treatment is given only to HLA-B*5701-negative persons because a strong predictive association between carriage of HLA-B*5701 and abacavir hypersensitivity reactions in Caucasian and Hispanic ethnic groups has been demonstrated.[3,7,8]

Management[3,6]:

The main principles of management are accurate diagnosis and risk assessment, followed by drug avoidance and reducing the risks of inadvertent administration.

1. Acute management: For some allergic drug reactions, withdrawal of the drug on a temporary or permanent basis may be all that is required for treatment. Anaphylactic reactions require prompt emergency treatment with the drugs like adrenaline, hydrocortisone, antihistaminics along with resuscitative measures.[1]
2. Drug desensitization: Desensitization in case of IgE-mediated reactions or graded challenge in non-IgE-mediated reactions is done with the drugs indispensable in the patient before next administration of the suspected drug. Drug desensitization should only be undertaken

by clinicians who are familiar with the procedure, and in particular it should be noted that this approach is never appropriate for patients who have experienced severe non-IgE mediated reactions (Stevens-Johnson syndrome, toxic epidermolysis, etc.).

3. Prevention: Prophylactic regimen is considered to be effective before administration of culprit drug. Some milder pseudo-allergic reactions can be suppressed by pretreatment with antihistaminics and corticosteroids. Patients should be advised to ensure their next of kin are aware of any important drug allergies and they may wish to carry information about drug allergies on their person, in the form of a Medicalert bracelet or locket. This is particularly relevant for drugs that might be given in an emergency setting where the patients might be unable to give a clear account of them.

4. Prudent use of drugs in future should be executed i.e. when the symptoms resolve, but if the clinical need for the drug remains valid, (example anti-TB drugs, penicillins in syphilis) it may be appropriate to reintroduce some or all of the medications. Where several drugs have been stopped, this would usually be done one drug at a time, starting with the drug thought most important for the patient's clinical care (as opposed to the one thought most likely to have caused the reaction). An interval of 48-72 hrs should be maintained before restarting the next drug.

Conclusion:

Hypersensitivity reactions are unpredictable; however awareness of the drugs known to cause HSR and vulnerable patients can reduce their incidence with good vigilance. Because of the generation of p-i concept most of the so-called unpredictable type B drug reactions might become the most predictable drug reactions and hence aid tailored medicine. Understanding of genetic predisposition to hypersensitivity reactions and advanced laboratory work up could help to decrease the severity of presentation of drug hypersensitivity reactions.

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PHARMACOVIGILANCE OF VACCINES: AN OVERVIEW

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Department Of Community Medicine

What is a Vaccine?

The process of conferring increased resistance (or decreased susceptibility) to infection is called as immunization and a 'Bio-preparation' intended to produce immunity to a disease by stimulating the production of antibodies is called a vaccine. Vaccine differs from the drug as it generates memory cells and trains the immune system to tackle the disease agent as against the drug which kills the invader pathogen or inhibits their growth.

Growing Market of Vaccines

Nearly 100 years after the advent of Small-pox vaccine there has been a surge in number of vaccines in the market (Figure 1). Looking at the trend of global vaccine market one realises the boom this industry has created. India is destined to become the "vaccine hub" of the world owing to the ever increasing demand coupled with the less cost of research and manufacturing of vaccines as compared to the west.[1]

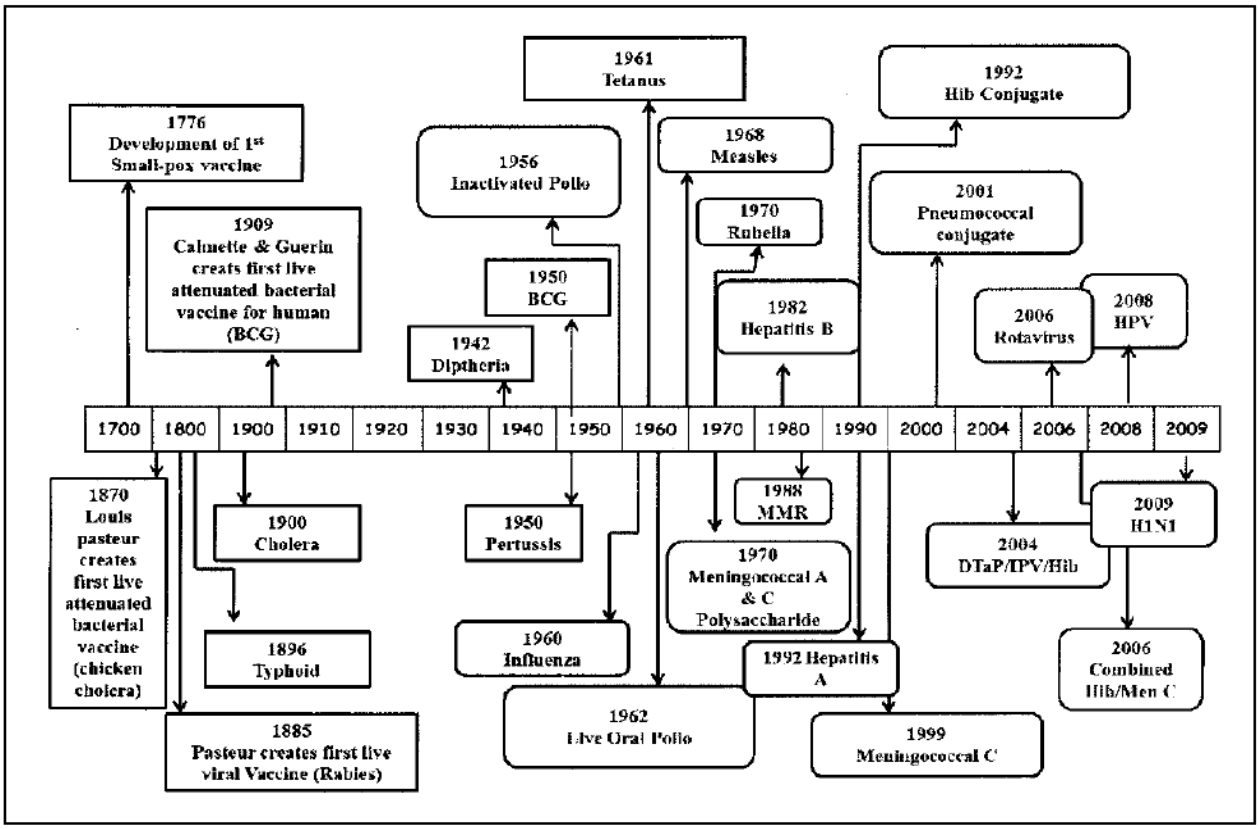

Figure 1 - Timeline of development of important vaccines

Vaccine Controversy

The "Vaccine controversy" is said to be a dispute over the morality, ethics, effectiveness, or safety of vaccinations. Globally there is lot of speculation in terms of vaccination as to what vaccines to give and what not to give.[2] The decision of whether to vaccinate or not on the basis of efficacy depends on the fact that the vaccine has been successful in significantly decreasing the incidence of the disease and can achieve a "sero-conversion" rate required for protection from the disease. There is lack of reliable epidemiological data on the existing level of immunity protection against diseases across India, with or without vaccination, or before and after vaccination.[3] Hence, the decision to include the vaccines in public health system will be more logical if done after conducting clinical studies.

The World Health Organization (WHO) has pointed out that people are becoming more and more concerned with the risk of adverse events associated with vaccines. There have been instances where adverse drug reactions (ADRs) related to vaccine has led to a huge hue and cry in the society. For example, false association of Sudden Infant Death Syndrome (SIDS or cot death) with immunization as SIDS incidence peaks around the age of early childhood immunization. Similarly there were speculations of MMR vaccination leading to autism and rising trend of asthma as a result of vaccination. However, controlled studies have shown that the association of these conditions with immunization is purely coincidental and not causal. Hence, there is a need for an effective monitoring system for both efficacy and safety of vaccines.

Adverse Drug Reactions Following Vaccination

ADRs are of great importance with respect to vaccines as they are used as preventive measures and not therapeutic measures in healthy individuals, particularly children. These vaccine related ADRs are called as adverse events following immunization (AEFI) and should be handled effectively in order to maintain/restore public faith in immunization programme.

Differences Between Surveillance of AEFIs and of ADRs

What drugs are to ill people, vaccines are to healthy people. Vaccines are administered voluntarily to healthy people for the prevention of disease, while most drugs are used to treat or control disease in ill people. Hence, the community is ready to bear much higher level of risk with drugs as compared to vaccines. Also, the implication of an adverse event is at larger scale for a vaccine, which is given to an entire cohort of the population, as compared to a drug. Moreover, with the decline of vaccine-preventable infectious diseases, the concern now shifts to the risks associated with vaccines. Even the assessment of causality differs in case of vaccine which requires expertise and understanding of immunization programmes. The priority is to identify

and correct programme errors and ascertain coincidental events to prevent setback to immunization programme. Thus, the monitoring system for vaccine related adverse events is much more sensitive. Single system of surveillance for both drug related ADR and AEFI can lead to overlooking the AEFI monitoring. Hence, it is mandatory to have different pathway for surveillance of AEFI.[4]

Adverse Events Following Immunization

An adverse event following immunization (AEFI) is defined as a medical incident that takes place after an immunization, causes concern, and is believed to be caused by immunization.[4] The causality assessment of AEFI (Figure 2) is done to decide whether an adverse event is actually caused by the vaccine following which it is classified into five categories ranging from a minor or common reaction to serious reactions which might result in death (Table 1).

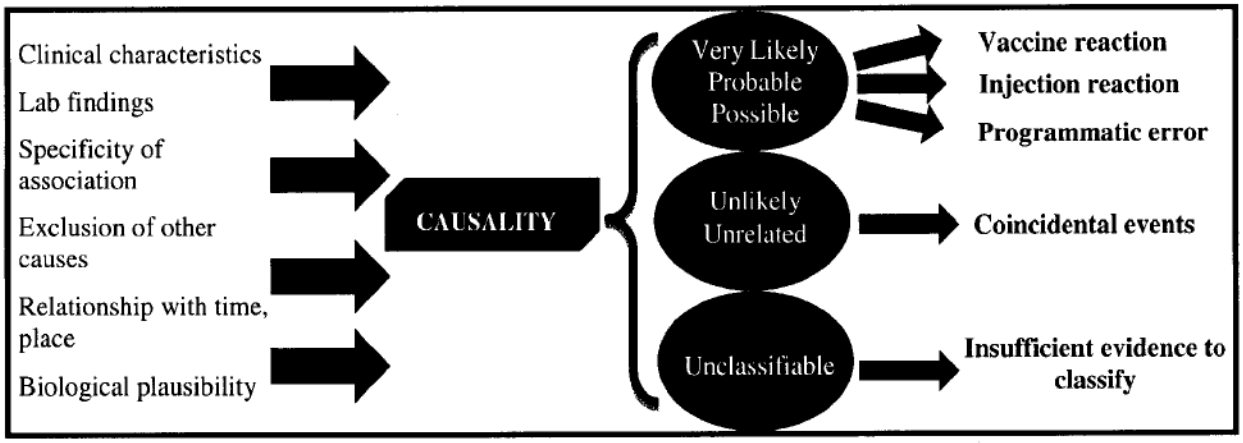

Figure 2 - Categories of causality using WHO causality assessment criteria[5]

Another aspect in vaccination is the increased use of multivalent or polyvalent vaccine for better coverage, compliance and effectiveness. A polyvalent vaccine is designed to immunize against two or more strains of the same microorganism, or against two or more microorganisms. Across the globe Pentavalent, Mixed and Hexavalent vaccines are being used. Such vaccines reduce the number of injections and hence the AEFI related to programme error gets minimized. However, there is a challenge of ascertaining the causality with such polyvalent vaccines as the adverse event cannot be linked to any one particular antigen. This not only makes the investigation problematic but the corrective measures are also difficult to carry out.

Table 1: Classification of Adverse Events Following Immunization[5]

Categories	Events	Type	Examples
Vaccine Reaction	Event caused or precipitated by the vaccine when given correctly, caused by inherent properties of vaccine	Common, minor vaccine reactions	Local - Swelling and / or redness at the injection site after DPT (whole cell)
			Systemic - Measles' vaccine causes fever, rash and / or conjunctivitis
		Rare, more serious vaccine reactions	Disseminated BCG infection after BCG vaccination
Programme Error	Event caused by an error in vaccine preparation, handling, or administration	Non-sterile injection	Reuse of disposable syringe or needle leading to abscess, toxic shock syndrome or blood-borne virus infection
		Vaccine prepared incorrectly	Vaccine reconstituted with incorrect diluent (Use of muscle relaxant instead of diluent) leading to hypotonia
		Vaccine injected in wrong site	Subcutaneous instead of intradermal injection for BCG leading to injection site abscess
		Vaccine transported / stored incorrectly	Increased local reaction from frozen vaccine
		Contraindica-tions ignored	Ignoring previous severe reaction like convulsions with DPT vaccine
Coincidental	Event that happens after immunization but not caused by the vaccine - a chance association	False association of SIDS or cot death with immunization	
Injection Reaction	Event from anxiety about, or pain from, the injection itself rather than the vaccine	Hyperventilation as a result of anxiety about the immuni-zation leads to specific symptoms (light-headedness, dizziness, tingling around the mouth and in the hands)	
Unknown	Event's cause cannot be determined	Does not fit any of the above types	

AEFI Surveillance System

AEFI surveillance is defined as detecting, monitoring and responding to adverse events following immunization (AEFI); implementing appropriate and immediate action to correct any unsafe practices detected through the AEFI surveillance system, in order to lessen the negative impact on the health of individuals and the reputation of the immunization programme.[5] The United States has the Vaccine Adverse Event Reporting System (VAERS) which is a national vaccine safety surveillance programme providing a nationwide mechanism to report AEFI. It acts as a vehicle for disseminating vaccine safety information and maintains a reliable database. As compared to this, in the developing countries the notification of the AEFI is poor and needs urgent streamlining of notification and investigation.

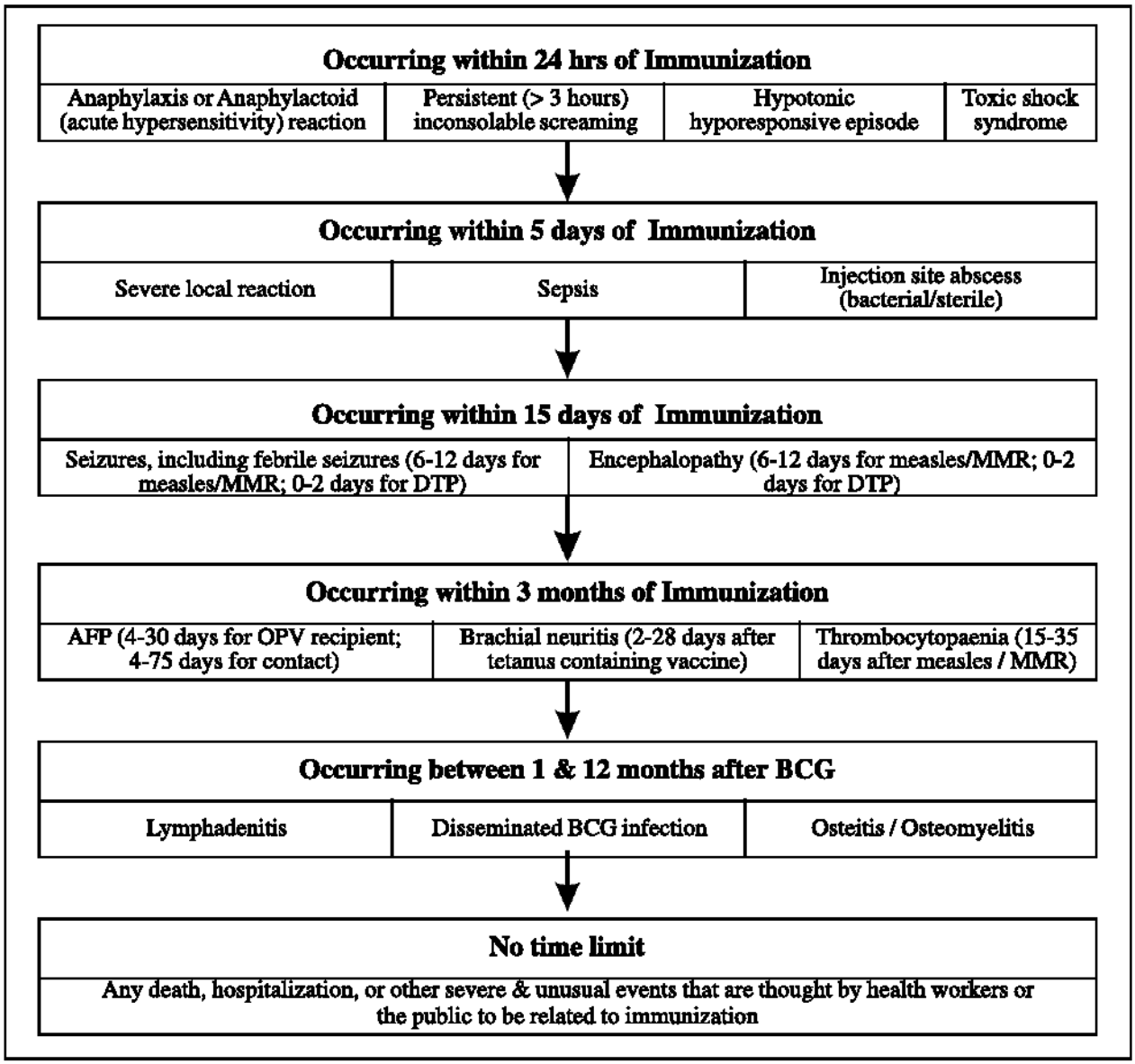

Figure 3 - What to Report : WHO Guidelines for Serious events [4]

[NOTE: Minor events (swelling and/or redness at the injection site, fever & self-limiting systemic symptoms) are reported monthly whereas the serious ones are to be reported immediately by the quickest means of communication. AFP : Acute Flaccid Paralysis]

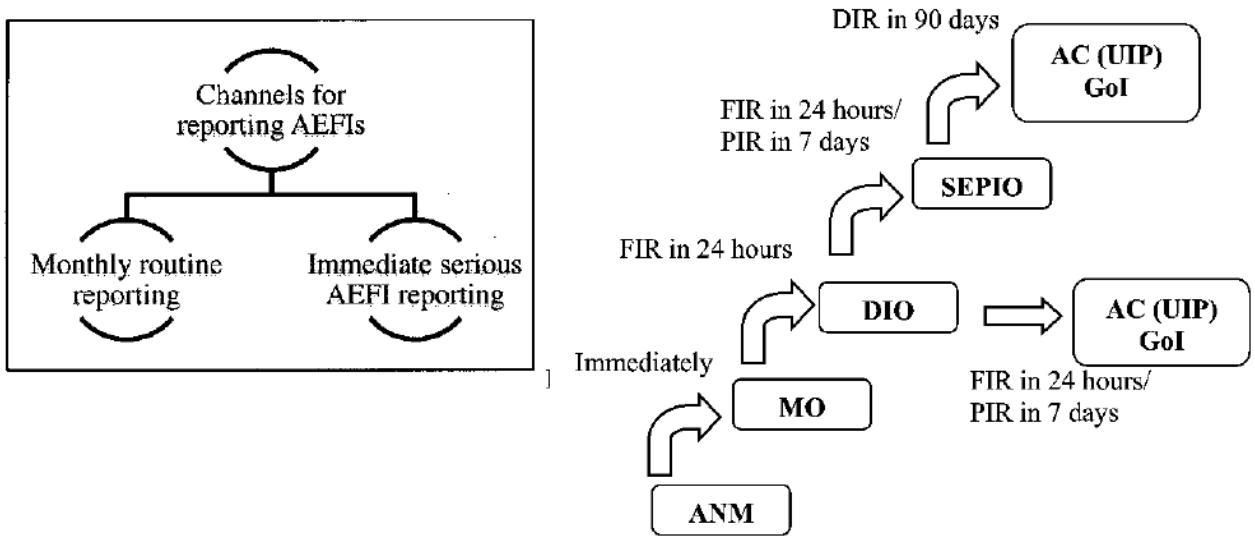

Figure 4 - How, Who, When to Report : WHO Guidelines for Serious events [4]

[NOTE: The monthly reporting includes both non-serious and serious AEFIs. ANM: Auxiliary Nurse Midwife; MO: Medical Officer; DIO: District Immunization Officer; SEPIO: State EPI Officer; AC (UIP) GoI: Assistant Commissioner (Universal Immunization Programme), Ministry of Health & Family Welfare, Government of India; FIR: First Information Report; PIR: Preliminary Investigation Report; DIR: Detailed Investigation Report]

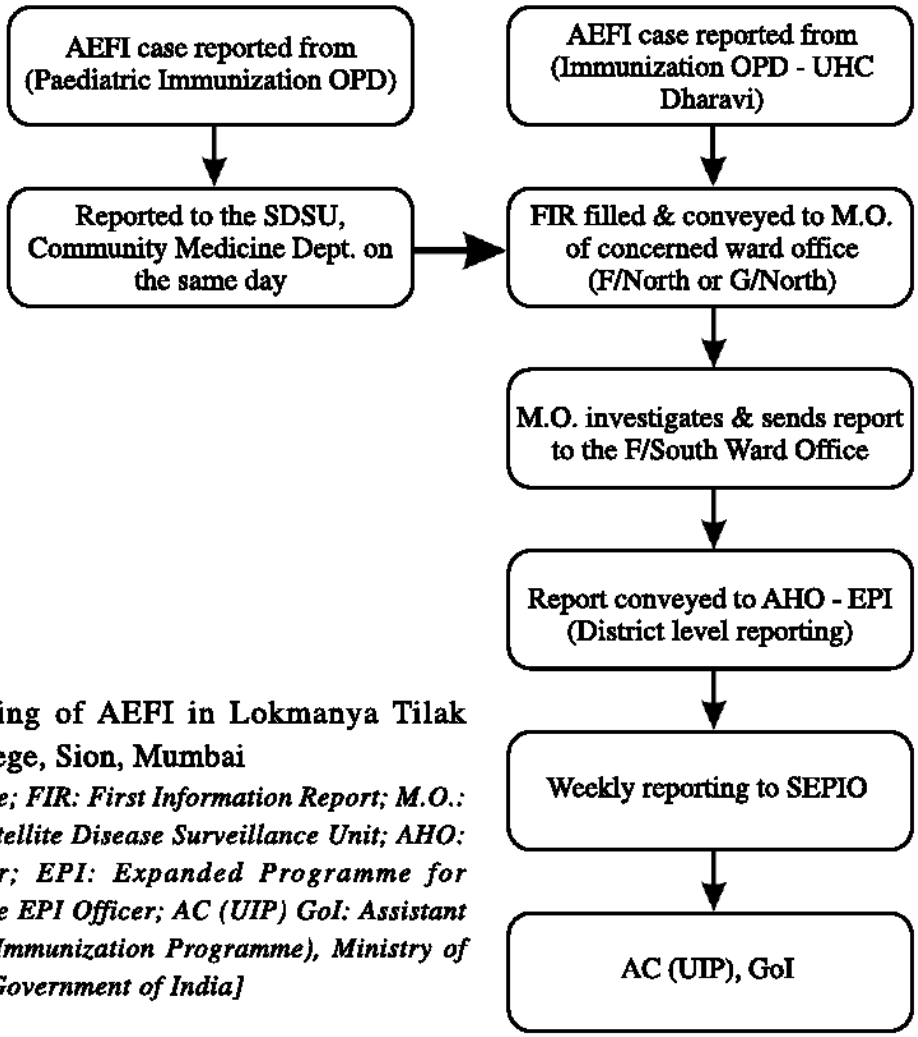

Figure 5 - The reporting of AEFI in Lokmanya Tilak Municipal Medical College, Sion, Mumbai

[UHC: Urban Health Centre; FIR: First Information Report; M.O.: Medical Officer; SDSU: Satellite Disease Surveillance Unit; AHO: Assistant Health Officer; EPI: Expanded Programme for Immunization; SEPIO: State EPI Officer; AC (UIP) GoI: Assistant Commissioner, (Universal Immunization Programme), Ministry of Health & Family Welfare, Government of India]

In India, the AEFI surveillance system started in 1986 which required the investigation of death and hospitalization due to immunization. Unlike the drug induced ADRs, it is mandatory now to report each and every AEFI, however, there is no public health act governing the same, whereby the defaulters can be held responsible and charged with the disciplinary action. WHO has given the guidelines regarding who, when, how and what in regards to AEFI reporting (Figure 3 & 4). In Mumbai this reporting is done through the Assistant Health Officer - Expanded Programme of Immunization (Figure 5).

Conclusion

The vaccine is the biggest achievement of medical science and preventive medicine. It is of great importance and the need can never be undermined. But the use of each and every vaccine has to be justified for mass immunization. The standards have to be set and strengthened with the double blind trials with appropriate follow up. The lucrative vaccine market should not be operating for business but for the humanitarian sake. Strict AEFI surveillance will not only ensure the vaccine safety but will determine the success of mass vaccination in coming days.

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LIST OF ADVERSE DRUG REACTIONS
(March 2012 - June 2012)

Sr. No.	Adverse Drug Reaction	Suspected Drugs	Causality Assessment	Literature Documentation
1	Hyperglycemia	Prednisolone, Budesonide	Possible	Well documented
2	Hepatotoxicity	Isoniazid, Rifampicin, Pyrazinamide, Ceftriaxone	Possible	Well documented
3	Hepatotoxicity	Chlordiazepoxide, Ethyl alcohol	Possible	Well documented
4	Angioedema	Diclofenac, Azithromycin	Possible	Well documented
5	Rash	Ofloxacin	Probable	Well documented
6	Cholestasis	Piperacillin, Tazobactum	Possible	Well documented
7	Phototoxicity	Chloroquine	Possible	Well documented
8	Nausea	Azithromycin	Probable	Well documented
9	Hypersensitivity	Iron Sucrose	Probable	Well documented
10	Peripheral Neuropathy	Lamivudine	Possible	Well documented
11	Anaphylaxis	Penicillin	Possible	Well documented
12	Hypersensitivity	Iron Sucrose	Probable	Well documented
13	Hypoglycemia	Insulin, Gliclazide, Metformin	Possible	Well documented
14	Giddiness	Rifampicin	Possible	Well documented
15	Hepatic Fibrosis	Methotrexate	Possible	Well documented
16	Anaemia	Zidovudine, Lamivudine	Possible	Well documented
17	Hypoglycemia	Glibenclamide	Probable	Well documented
18	Fixed drug eruption	Carbamazepine, Rituximab, Azathioprine, Baclofen, Amitryptiline, Pregabalin	Possible	Documented for Carbamazepine
19	Rash	Piperacillin, Tazobactam, Vancomycin	Possible	Well documented
20	Gum Hypertrophy	Phenytoin	Possible	Well documented
21	Hepatic Failure	Isoniazid, Rifampicin, Pyrazinamide	Possible	Well documented
22	Stevens Johnson Syndrome	Methotrexate	Probable	Well documented
23	Rash	Efavirenz, Zidovudine, Lamivudine	Possible	Well documented
24	Rash	Cefotaxime, Tetanus toxoid	Possible	Well documented
25	Rash	Cefotaxime, Amikacin, Chloroquine	Possible	Well documented
26	Rash	Artesunate	Possible	Well documented
27	Anaemia	Zidovudine, Lamivudine	Possible	Well documented
28	Anaemia	Zidovudine, Lamivudine	Possible	Well documented
29	Rash	Amoxicillin, Clavulanic acid, Ibuprofen	Possible	Well documented
30	Hemoptysis	Warfarin	Probable	Well documented
31	Stevens-Johnson Syndrome	Leflunomide	Possible	Well documented
32	Hepatotoxicity	Leflunomide	Possible	Well documented
33	Periorbital puffiness	Amoxicillin, Metronidazole, Paracetamol	Unlikely	Not documented
34	Hypotension	Azithromycin	Probable	Documented

35	Hematuria, Hemoptysis, Ecchymotic Patches	Warfarin, Aspirin	Possible	Interaction documented
36	Raised liver enzymes	Amoxicillin, Clavulanic acid	Possible	Well documented
37	Rash	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol	Possible	Well documented
38	Nausea, Vomiting	Zidovudine, Lamivudine, Nevirapine, Co-trimoxazole	Possible	Well documented
39	Nail Hyperpigmentation	Zidovudine	Possible	Well documented
40	Rash	Co-trimoxazole, Efavirenz, Zidovudine, Lamivudine, Pyrazinamide, Rifampicin, Ethambutol, Isoniazid, Azithromycin	Possible	Well documented
41	Hepatotoxicity	Isoniazid, Rifampicin, Pyrazinamide	Possible	Well documented
42	Rash	Nevirapine, Zidovudine,Lamivudine, Chloroquine, Paracetamol	Possible	Well documented
43	Angioedema	Chloroquine, Piperaquine, Arterolane	Possible	Well documented
44	Rash	Amoxicillin, Metronidazole, Pantoprazole	Possible	Well documented
45	Gastric Irritation	Diclofenac, Metronidazole	Possible	Well documented
46	Anaphylaxis	Gelofusine, Propofol, Cefotaxime, Midazolam, Fentanyl, Glycopyrolate, Tranexamic acid	Possible	Well documented
47	Anaemia	Zidovudine, Lamivudine, Co-trimoxazole, Fluconazole	Possible	Well documented
48	Convulsions	DPT Vaccine	Possible	Well documented
49	Rash	Ceftriaxone	Probable	Well documented
50	Cushing's syndrome	Prednisolone	Probable	Well documented
51	DRESS Syndrome	Phenytoin, Pyrazinamide, Rifampicin, Isoniazid	Possible	Well documented
52	Angioedema	Paracetamol, Nimesulide, Ofloxacin, Metronidazole	Possible	Well documented
52	Haematemesis	Paracetamol, Dicyclomine	Possible	Well documented
53	Rash	Vancomycin, Pyrazinamide, Rifampicin, Isoniazid, Ethambutol, Piperacillin, Tazobactam, Amikacin	Possible	Well documented
54	Anaemia	Zidovudine	Possible	Well documented
55	Hepatotoxicity	Isoniazid, Rifampicin, Pyrazinamide	Possible	Well documented
56	Hematuria	Warfarin, Clopidogrel, Aspirin, Diltiazem	Possible	Drug interaction Well documented
57	Rash	Doxycycline, Artemether, Lumefantrine, Paracetamol, Ondansetron, Ranitidine	Possible	Well documented
58	Herpes labialis	Prednisolone	Possible	Well documented
59	Impaired renal function	Amikacin	Possible	Well documented
60	Gastritis	Iron sulfate, Clindamycin	Possible	Well documented
61	Haematemesis	Warfarin	Probable	Well documented
62	Stevens Johnson syndrome	Ampicillin, Paracetamol	Possible	Well documented
63	Thrombocytopenia	Rifampicin	Probable	Well documented
64	Toxic epidermal Necrolysis	Amoxicillin	Possible	Well documented
65	Rash	Nitrofurantoin, Ceftriaxone, Paracetamol, Pantoprazole	Possible	Well documented
66	Thrombocytopenia	Piperacillin, Ceftazidime, Metronidazole, Tramadol	Possible	Well documented

EVALUATION OF A CASE FROM LTMMC AND LTMGH

Hepatotoxicity in a Patient with Psoriasis on long term Methotrexate

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We present a case of 72 years old non-alcoholic male who was suffering with psoriasis for last 15 years and was prescribed methotrexate and folic acid by his treating physician. His psoriatic lesions were within control with 10 mg weekly methotrexate dose which he had been taking for last 7 years. He was also taking Tab metformin since last 10 months for diabetes mellitus.

One year before presenting to our hospital, he had 3 episodes of abdominal distension and pedal edema, for which his methotrexate was stopped and treated in some private set up. In October 2011, he presented to our hospital with aggravated symptoms of abdominal distension and pedal edema.

On examination, his psoriatic plaques had recurred over his legs, forearms, abdomen and back. There was mild pallor, icterus and pitting pedal edema. His abdomen was distended and tender with shifting dullness. Rest of the general and systemic examinations were essentially normal. Biochemical estimation, liver function studies showed total bilirubin of 1.6 mg/dl, direct bilirubin of 0.8 mg/dl, total protein 5.2 gm/dl, serum albumin2.3 gm/dl, SGOT 84 IU/l and SGPT 80 IU/l. Viral markers (HBs Ag, Anti HCV) were non-reactive. Previous records of investigations were not available for comparisons. Ultrasonography of abdomen showed small sized liver with coarse parenchymal echotexture and nodular surface outline suggestive of cirrhosis.

Discussion:

Methotrexate (MTX) has been approved by the Food and Drug Administration (FDA) for psoriasis since 1972.[1] MTX possesses potent anti-inflammatory action as it inhibits proliferation or induces apoptosis in activated T-cells and blocks the abnormal rapid epidermal cell proliferation, both responsible for the characteristic skin lesions in psoriasis.[2] In the past decade, biologic agents like alefacept, efalizumab, etanercept, infliximab, and adalimumab have been approved by the FDA for the treatment of psoriasis. However, methotrexate still remains a less costly option.

Within the recommended cumulative dose, MTX is considered to be a relatively safe drug.

However, it causes some important systemic toxicity, namely, hepatotoxicity, myelosuppression and pulmonary fibrosis. Other adverse effects include stomatitis, oral ulcers, anorexia, malaise, renal insufficiency and teratogenesis.

The pathogenesis of MTX-induced hepatic damage is poorly understood. Few of the studied mechanisms include, methotrexate induced release of endogenous adenosine, suppression of metalloproteinases MMP-9 and MMP-14[3], accumulation of polyglutamate forms of the MTX in hepatocytes,[4] and inhibition of cytosolic nicotinamide adenosine diphosphate (NADP)-dependent dehydrogenase and NADP malic enzymes.[5-9]

Risk factors for hepatic toxicity due to methotrexate therapy in psoriasis are alcohol consumption, obesity, hyperlipidemia, diabetes, previous exposure to liver toxins, and hepatitis. Patients with low risk are monitored as per the American College of Rheumatology guidelines (Table 1) while patients with high risks are monitored with stringent guidelines (Table 2).[10] In the current case, diabetes was present as a risk factor. A study by Malatjalian DA. et al showed that diabetic patients with psoriasis are particularly at increased risk of MTX hepatotoxicity.[11]

Table 1 : Monitoring in low risk patients

No baseline liver biopsy
Monitor LFT 1-2 monthly :
(i) For minor elevations (<2ULN), repeat in 2 to 4 weeks.
(ii) For moderate elevations (>2-fold but >3ULN), repeat in 2 to 4weeks, and dose reductions as necessary.
(iii)For persistent elevations in 5 of 9 AST levels over a 12-month period, perform a liver biopsy.
Consider continuing to follow according to above ACR guidelines without biopsy OR
Consider liver biopsy after 3.5 to 4.0 g total cumulative dosage OR
Consider switching to another agent or discontinuing therapy after 3.5 to 4.0 g total cumulative dosage.

 # ULN : upper limit of normal

Table 2: Monitoring in high risk patients

Consider the use of a different systemic agent
Consider delayed baseline liver biopsy (after 2 to 6 months of therapy to establish medication efficacy and tolerability).
Repeat liver biopsies after approximately 1.0 to 1.5 g of therapy.

Another known cause for hepatitis in psoriatic patients is non-alcoholic steatohepatitis (NASH). NASH is usually a silent disease and may take many years to manifest and it may be difficult to differentiate it from MTX induced hepatitis. However it is known that the symptoms of NASH with co-existing risk factors of obesity and diabetes may be aggravated by MTX therapy.[10,12]

The histopathologic features of methotrexate induced liver toxicity resemble non-alcoholic steatohepatitis (NASH), except that the latter is not associated with fibrosis and dystrophic nuclei.[13]

As per the guidelines, liver biopsy and histopathologic examination is recommended for patients with 3.5 to 4.0 g of cumulative methotrexate.[10] Langman G et al found a positive correlation between the cumulative dose, risk factors and progression of liver injury.[14]

In the present case, even though the cumulative dose of MTX given was 3.36gm, biopsy was not performed on admission as advanced age was a contraindication. Moreover biopsy was also not performed in the private set up where the patient initially followed up. Thus, there was no confirmation of diagnosis or differentiation of MTX induced hepatitis from NASH hence as per the WHO scale, the causality of this ADR can be graded as 'Possible' for MTX.

Adequate measures should be taken for the prevention of adverse effects due to MTX. Non-invasive tests have been used for screening liver fibrosis and cirrhosis (PIIINP, Fibrotest, Fibroscan).[15] The type III pro-collagen (PIIINP) is being used an indicator of fibrogenesis, reducing the number of liver biopsies by 7-fold. In developing countries, where advanced noninvasive methods for the assessment of liver damage are unaffordable or unavailable, Kumar et al suggested tapering off of MTX when the disease subsides in response to treatment combined with natural/seasonal remission. Intensive topical & heliotherapy (light/phototherapy) facilitates earliest possible withdrawal and the longest possible drug-free interval before the next relapse.[16] Combination therapy of lower doses of MTX with cyclosporine or biologic agents have been proven to be effective, thus, facilitating lower cumulative dosage of MTX and hence reduced adverse effects.[17,18] Concomitant Ursodeoxycholic Acid (UDCA) treatment has been shown to be protective against methotrexate-induced liver toxicity.[19-21] Folic acid supplementation also reduces hepatotoxicity along with hematologic and gastrointestinal adverse effects without decreasing the efficacy.[22]

Conclusion

Methotrexate remains an effective treatment, used alone or in combination with biologics for the treatment of psoriasis, and many other conditions. While on methotrexate therapy, patient should be educated about the need for close follow-up and monitoring for toxicity. Rational patient selection and regular, prompt and appropriate monitoring helps in improving the safety and efficacy of this drug.

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PUBLISHED CASE REPORTS / STUDIES ON METHORTEXATE INDUCED LIVER DAMAGE

Dr. Jaisen Lokhande, *Assistant Professor, Department of Pharmacology*

A liver fibrosis cocktail? Psoriasis, methotrexate and genetic hemochromatosis.

BMC Dermatol 2005 Nov 29;5:12.

Mathew J, Leong MY, Morley N, Burt AD

Background: Pathologists are often faced with the dilemma of whether to recommend continuation of methotrexate therapy for psoriasis within the context of an existing pro-fibrogenic risk factor, in this instance, patients with genetic hemochromatosis.

Case Presentations: We describe our experience with two male psoriatic patients (A and B) on long term methotrexate therapy (cumulative dose A = 1.56 gms and B = 7.88 gms) with hetero- (A) and homozygous (B) genetic hemochromatosis. These patients liver function were monitored with routine biochemical profiling; apart from mild perivenular fibrosis in one patient (B), significant liver fibrosis was not identified in either patient with multiple interval percutaneous liver biopsies; in the latter instance this patient (B) had an additional risk factor of partiality to alcohol.

Conclusion: We conclude that methotrexate therapy is relatively safe in patients with genetic hemochromatosis, with no other risk factor, but caution that the risk of fibrosis be monitored, preferably by non-invasive techniques, or by liver biopsy.

Acute hepatic necrosis in a case of acute cholecystitis

Grand Rounds 2008;8:14-18

Jason A. Bolton, Bijendra Patel and Hannah Simms

A 73-year-old Asian gentleman was admitted via the Accident and Emergency Department with upper abdominal pain, jaundice, fever and rigors. Past history included non-insulin dependent diabetes, asthma, psoriasis and alcoholism. His drug history included methotrexate. A diagnosis of acute cholecystitis was made and ultrasound findings were consistent with this. The patient started to improve but on day 8 of his admission he suddenly deteriorated and arrested. The post mortem revealed complete hepatic necrosis as an unexpected cause of death. There are a number of factors which may be contributory in this case. The fact that our patient expired so rapidly with complete hepatic necrosis was not in keeping with the typical chronic course one might expect. We should always bear in mind the potential for fatal hepatic injury in patients presenting with hepatobiliary symptoms with a past history of alcohol abuse and methotrexate therapy.

Methotrexate and liver function: a study of 13 psoriasis cases treated with different cumulative dosages.

J Eur Acad Dermatol Venereol. 2008 Jan;22(1):25-9.
Carneiro SC, Cássia FF, Lamy F, Chagas VL, Ramos-e-Silva M.
Background: The need and frequency of hepatic biopsies during methotrexate (MTX) therapy are still controversial.
Objectives: The purpose of this investigation is to assess MTX liver toxicity in patients with psoriasis through percutaneous liver biopsy, and compare liver morphology changes with increasing cumulative dosages (1, 2, 3 and 4 g) of MTX.
Results: Cumulative dosages of 1 to 2 g MTX did not cause significant liver toxicity. From a cumulative dosage of 3 to 4 g, there is fibrosis formation, inflammation enhancement in the portal area and fibrous septa, configuring regenerative nodes.
Conclusion: In patients with no risk factors for liver disease, with normal physical examination and liver tests, biopsy can be done after a cumulative MTX dosage of approximately 1 to 1.5 g and repeated for each gram. In patients with risk factors, liver biopsy should be done before use of MTX, or within the first 2 months of treatment at the most, and repeated for each gram of cumulative dosage.

Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury.

J Gastroenterol Hepatol. 2001 Dec;16(12):1395-401.
Langman G, Hall PM, Todd G.
Background and Aims: Hepatotoxicity, especially liver fibrosis, is the major concern with long-term, 'low-dose' oral methotrexate (MTX) therapy for psoriasis. The histological features are non-specific and resemble those of non-alcoholic steatohepatitis (NASH). Moreover, most of the risk factors of MTX-induced liver injury are also associated with NASH. In this study, we investigate whether NASH contributes to the prevalence and progression of MTX-induced liver injury in patients receiving MTX for psoriasis.
Methods: Clinical details, including MTX dosage schedules and risk factors for liver injury, was documented for 24 patients on long-term MTX therapy for psoriasis. Serial liver biopsies were graded according to the Roenigk classification scale and a recently proposed grading and staging system for NASH.
Results: Thirteen of the 17 patients who had a NASH-like pattern of liver injury also had the risk factors for NASH obesity and/or diabetes, and all had progressive liver injury. The other four patients had no risk factors, but a mean cumulative dose of 6.5 g. Seven patients, who did not have a NASH-like pattern of injury, had a mean cumulative dose of 3.8 g. There was a positive correlation between the cumulative dose, risk factors and progression when the biopsies were scored by the modified grading and staging classification for NASH, but not with the Roenigk system.
Conclusions: Non-steatohepatitis, probably aggravated by MTX, is an important cause of liver injury in patients on long-term, 'low-dose' MTX treatment for psoriasis. In addition, MTX alone can cause a NASH-like pattern of injury that is, in part, caused by a higher cumulative dose.

REGULATORY UPDATE

Dr Girish Joshi*, Dr Kalpesh Dalvi**

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FDA Approvals: Combo Meningitis Vaccine for Infants

The US Food and Drug Administration (FDA) has approved a combination meningitis vaccine for infants and children aged 6 weeks through 18 months. The FDA said this is the first meningococcal vaccine that can be taken by children as young as age 6 weeks. The vaccine immunizes against 2 types of bacteria: N meningitidis (serogroups C and Y) and Hib.

Their immune responses to the Hib component resembled those of infants and toddlers who received a vaccine against invasive Hib disease. The combination vaccine also produced antibodies against the meningococcal component at levels, indicating that it would offer protection against meningococcal disease caused by serogroups C and Y of N meningitidis.

The vaccine's safety was established by a study of roughly 7500 infants and toddlers in the United States, Mexico, and Australia. Pain, redness, and swelling at the injection site; irritability; and fever were common adverse reactions.

The combination meningitis vaccine is administered in 4 doses at months 2, 4 and 6, with the fourth dose administered between months 12 and 16. The first dose can be given as early as age 6 weeks, and the last as late as age 18 months.

Adverse Reactions: Depending on reaction and specific dose in the vaccination schedule, rates of local injection site pain, redness, and swelling ranged from 15% to 46%. Commonly reported systemic adverse reactions included irritability in 62% to 71% of children, drowsiness in 49% to 63%, loss of appetite in 30% to 34%, and fever in 11% to 26%. Also, the specific rate varied according to the event and dose in the schedule.

Adapted from : Lowes R and Barclay L. FDA Approvals: Combo Meningitis Vaccine for Infants. [homepage on the Internet]. 2012 [cited 2012 July 20]. Available from: http://www.medscape.org/viewarticle/766119

CROSSWORD-I

ALPHABET 'B' PUZZLE

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**Assistant Professor, **Associate Professor, Department of Pharmacology*

1B									
2	B								
3		B							
4			B						
5				B					
6					B				
7						B			
8							B		
9								B	
10									B

Questions'

1. Hyperlipidemia & hypothyroidism are seen with this retinoid derivative used for treatment of Cutaneous T cell Lymphoma.
2. Addition of Adrenaline to Xylocaine solution reduces its _____ into general circulation thereby prolonging its local anaesthetic effect & reducing its systemic toxicity.
3. Somnolence & dizziness are the most common ADRs of this GABA analog having both antiseizure & analgesic properties.
4. Toxic doses of this uricosuric drug can lead to nephrotic syndrome & convulsions.
5. Insulin resistance, usually seen with beef or pork insulin, occurs due to development of _____ to contaminating proteins in the preparation.
6. Dysphoria & hallucinations are the major adverse effects of this cannabinoid receptor agonist used for treatment of chemotherapy induced vomiting.
7. This antiobesity drug was withdrawn from market due to its tendency to cause CNS depression including suicidal ideation.
8. Long term use of Metformin can lead to deficiency symptoms of this vitamin.
9. Benzodiazepines & Lithium, when taken during pregnancy, have been shown to cause _____ syndrome in the neonate causing it to go limp & drowsy with reduced breathing & suckling abilities.
10. Peripheral neuropathy is one of the important ADRs seen with this proteasome inhibitor used for treatment of refractory multiple myeloma.

Answers to Crossword-I

1) Bexarotene 2) Absorption 3) Gabapentin 4) Probenecid 5) Antibodies 6) Dronabinol 7) Rimonabant 8) Vitamin B12 9) Floppy Baby 10) Bortezomib

Answers to Crossword-II

Across: 1) PCOS-Polycystic Ovarian Syndrome 2) BCG-Bacillus Calmette Guerin 3) Cheese 4) Bone 5) MAO-Mono Amine Oxidase 6) Cilostazole 7) ACE-Angiotensin Converting Enzyme 8) OTO 9) DLE-Discoid Lupus Erythematosus 10) RIFA 11) Senna 12) NMDA-N-Methyl D-Aspartate 13) GTN-Glyceryl Trinitrate

Down: 14) SC-Subcutaneous 15) Zonisamide 16) Cefotetan 17) Obesity 18) Seizures 19) EMG-Electro Myo Gram 20) Gabapentin

CROSSWORD-II

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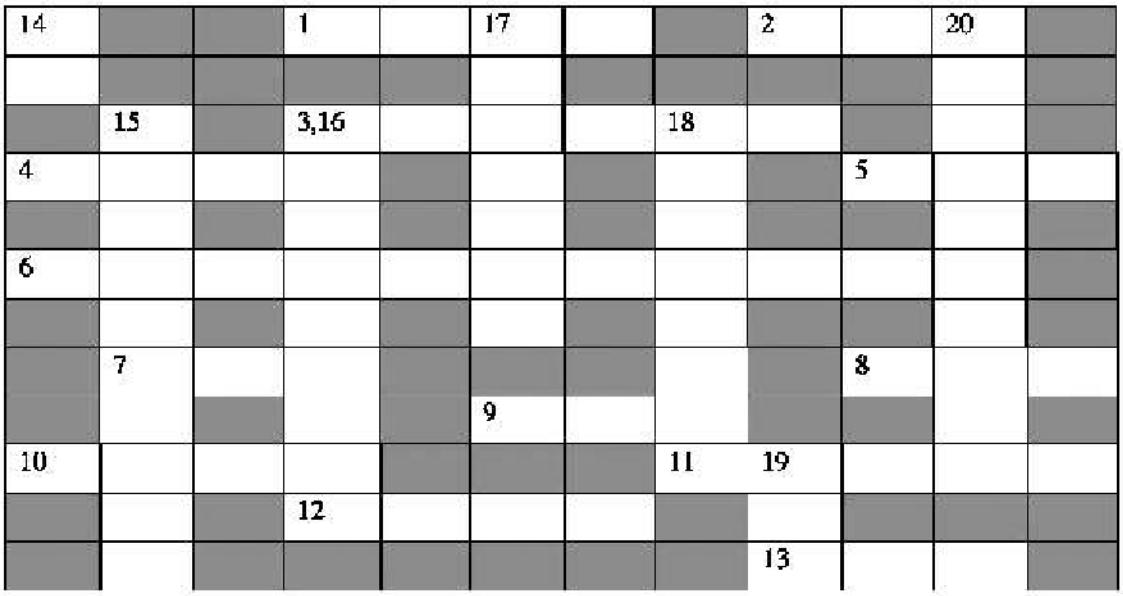

Across'

1. _____is one of the major adverse effects of hMG due to stimulation of too many ovarian follicles, when given for ovulation induction in females.(4)
2. Hypersensitivity reactions are one of the important ADRs seen when intravesical _____ is given to treat superficial bladder carcinoma.(3)
3. Linezolid is a reversible inhibitor of MAO enzyme and may lead to _____ reaction with food containing Tyramine.(6)
4. Bisphosphonates are administered to reduce steroid induced _____wasting.(4)
5. Postural hypotension, especially seen in elderly and minimised by slow dosage titration, is one of the important ADRs seen with _____inhibitors.(3)
6. Unlike Dipyridamole, _____, a congener of Dipyridamole, does not show 'Coronary Steal Phenomenon' and thus it is used as an adjuvant drug in antianginal therapy.(11)
7. Though _____inhibitors are not teratogenic during first trimester of pregnancy, their administration during second & third trimesters carries the risk of fetal malformations.(3)
8. The Aminoglycoside induced _____toxicity is worsened by coadministration of Vancomycin and lessened by calcium.(3)
9. _____is an example of iatrogenic disease caused by prolonged use of Hydralazine in high doses.(3)
10. Fluconazole, when co administered with _____butin, increases its plasma concentration resulting in Polymyalgia syndrome.(4)
11. Chronic use of _____, an irritant purgative, leads to a characteristic brown pigmentation of colon known as 'Melanosis coli'.(5)
12. Antiepileptic drug Felbamate, which acts through blockade of _____ receptors in brain, is associated with unpredictable aplastic anemia & hepatotoxicity.(4)
13. Tolerance develops rapidly when_____ is used orally, transdermal or by IV infusion without any drug free interval.(3)

Down'

14. Lipodystrophy occurring at the site of _____injection by Insulin, can be avoided by changing the injection sites.(2)
15. Urolithiasis is an adverse effect seen with Topiramate& _____ due to inhibition of carbonic anhydrase enzyme.(10)
16. Coagulation abnormalities due to this Cefamycin having N-methyl thiotetrazole side chain at R2 ,occurs due to destruction of vitamin K producing bacteria & reduction in synthesis of vitamin K dependent clotting factors.(9)
17. ADRs like CNS depression is seen with Rimonabant, which is a cannabinoid receptor antagonist previously indicated for treatment of _____ .(7)
18. The newer Carbapenems are safer than Imipenem because they do not cause _____, which are seen with Imipenem.(8)
19. Regular _____monitoring should be done when neuromuscular blockers are given in patients receiving Aminoglycosides.(3)
20. Weight gain & ataxia are some important ADRs seen with this antiepileptic drug which is used as a first line therapy for pain due to diabetic neuropathy & postherpetic neuralgia.(10)

Answers on page 23

We would like to request all the departments to contribute in ADR reporting.

Please feel free to contact us for the same.

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