ALL INDIA INSTITUTE OF MEDICAL SCIENCES, MANGALAGIRI

**PHARMACOLOGY BULLETIN**

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## FROM THE EDITORIAL DESK….

Dear Friends, Greetings from Department of Pharmacology and welcome to the 25th issue of ESSENCE

The results of a clinical trial are measured by its end points. These end points directly measure the outcome of clinical interest and are selected by investigators to assess the efficacy of a new drug or intervention. However, on many occasions, the investigators might select a surrogate end point based on the evidence that changes in these might reflect the changes in the clinically meaningful endpoints. The current issue of ESSENCE has an article discussing this important aspect.

Clinical Data Management (CDM) is an essential component of clinical research, focusing on the collection, storage, and analysis of data generated in clinical trials. This issue also talks about certain important aspects and terminologies used in CDM.

The current issue of ESSENCE also has a guest article on 'non-parametric tests' and their applications as important tools in statistical analysis particularly when the data do not meet the assumptions for parametric tests.

Further, as always, the current issue has new drug approvals, interesting news from the world of medicines, crossword puzzle on “Drug Induced Autoimmune Hepatitis' and the 'cartoon corner'.

We hope you enjoy reading it. Jai Hind.



Feedback and Suggestions may be sent to Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh at email id: pharmacology@aiimsmangalagiri.edu.in

The results of a clinical trial are measured by its endpoints. Endpoints that directly measure the clinical outcome of interest might be selected by investigators in a trial to assess the effectiveness of a novel medical product or a new usage for an existing one. Endpoints of the clinical studies may be surrogate endpoints or clinical outcomes. Clinical outcomes provide a direct indicator of how well study participants feel, perform, or live longer. A therapy's benefit or likely benefit is evaluated to see if it overcomes any side effects, such as drug-induced liver injury, based on clinical outcomes (such as improved symptoms). On the other hand, "A surrogate endpoint of a clinical trial is a laboratory measurement or a physiological sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives. Changes induced by therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint."

The salient features of surrogate endpoints are as follows

- Biologically plausible
- Measurable in all patients with the disease
- Predictive of disease progression
- Subject to standardization
- Reproducible
- Effect of treatment on surrogate endpoint should translate into effect on true endpoint

**Validation of Surrogate Endpoints:**

A surrogate endpoint's predictiveness is typically assessed by analysing scientific evidence related to pathophysiology, treatment, epidemiology, or other fields. Surrogate endpoints can be characterized by the level of clinical validation:

- Candidate surrogate endpoint
- Reasonably likely surrogate endpoint
- Validated surrogate endpoint

While validated surrogate endpoints have a strong clinical data base and a well-defined mechanistic reasoning supporting their prediction of a particular clinical benefit, candidate surrogate endpoints are still being evaluated for their capacity to do so.

Before a surrogate endpoint is approved as a replacement for a clinical outcome, extensive testing and evidence collection are required. Clinical trials and epidemiological research are two examples of evidence. Clinical trials must, above all, demonstrate that a surrogate endpoint correlates and is a valid predictor of the clinical effect. The FDA refers to a surrogate endpoint as validated if it has gone through this validation process and recognises it as proof of benefit. A well-known example of a surrogate endpoint is blood pressure with the relevant clinical endpoint being a stroke. Other examples are as follows

| Surrogate endpoint | Clinical endpoint |
|---|---|
| HIV viral load | Irreversible morbidity or mortality |
| Radiographic evidence of tumor shrinkage | Overall survival |
| Laboratory test showing clearance of bacteria from blood stream | Clinical resolution of infection |

**Are surrogate endpoints important for medical product development?**

Drug development programmes can generally operate more efficiently when surrogate endpoints are used, especially when they can reliably anticipate a positive effect through relevant research. For instance, numerous clinical trials utilising a variety of blood pressure-reduction drugs have shown that lowering systolic blood pressure decreased the risk of stroke. Therefore, utilising this validated surrogate endpoint, clinical studies aimed at reducing the risk of stroke can be carried out more quickly in smaller populations. The measurement of reduction in the surrogate endpoint of systolic blood pressure can therefore serve as a stand-in for the clinical result of stroke.

**Advantages of Surrogate Endpoints:**

- Promotes quicker assessment of treatment effects;
- Allows for smaller sample sizes in trials;
- Aids in the screening of novel treatments and expedites approval

**Pitfalls of Surrogate Endpoints:**

When the pathophysiology of the disease and the intervention's mechanism of action are well understood, surrogate endpoints are most likely to be beneficial. If not, pitfalls lie ahead.

- May not be a reliable indicator of clinical success;
- May have more negative impacts than positive ones;
- May not be appropriate for all patient demographics or disease stages;
- May still require follow-up for a "true endpoint"

For instance, smoking causes lung cancer, and a trial of the benefit of education in preventing lung cancer might use smoking as a surrogate endpoint rather than the occurrence of the cancer itself. On the other hand, if chemotherapy is used as a measure for treating lung cancer, smoking could not be used as a surrogate endpoint. This is obvious, but alerts us to the possibility of similar but less obvious examples, in which the mechanisms are not understood.

Antiarrhythmic medications stop ventricular arrhythmias, which are the cause of sudden death. Antiarrhythmic medications were therefore predicted to prevent unexpected death. Indeed, Class I antiarrhythmic medications markedly increased unexpected death in patients with asymptomatic ventricular arrhythmias following myocardial infarction in the Cardiac Arrhythmia Suppression Trial; as a result, the trial was terminated early. The theory was incorrect.

Surrogate endpoints may have little value if confounding variables are present. For instance, in patients with hyperthyroidism, serum T3 is utilised as a measure of the tissue damage caused by thyroid hormone. Its effectiveness is lessened in people on amiodarone, though, as this medication prevents T4 from being converted to T3 without necessarily changing thyroid function.

Clinical trials may be expedited and rendered more effective by using surrogate endpoints. On the other hand, the use of the surrogate endpoints may produce findings that are deceptive if it is not clearly linked to definitive milestones.

**Reference:** Aronson JK. Biomarkers and surrogate endpoints. Br J Clin Pharmacol. 2005 May;59(5):491-4.

## Recent new/Update from the world of medicines ….

**FDA Approved Sotatercept, First-in-Class Agent for Pulmonary Arterial Hypertension**

Sotatercept is a drug that is being developed to treat pulmonary arterial hypertension (PAH) and has been approved by FDA in March 2024). It is a soluble fusion protein that traps activin and other TGFβ ligands, which dampens signaling. Sotatercept works by binding the extracellular domain of activin receptor type IIA to the Fc portion of human IgG1. Sotatercept traps activin and other TGFβ ligands, which dampens signaling. This pathway is central to what is thought to be the alteration in PAH. The approval is based on the Phase 3 STELLAR trial, which compared WINREVAIR (n=163) to placebo (n=160), both in combination with background standard of care therapies in adult patients with PAH (WHO Group 1 FC II or III). Results showed adding WINREVAIR to background therapy increased six-minute walk distance from baseline by 41 meters (95% CI: 28, 54; p<0.001; placebo-adjusted) at Week 24 and significantly improved multiple important secondary outcome measures, including reducing the risk of death from any cause or PAH clinical worsening events by 84% versus background therapy alone (number of events: 9 vs 42, hazard ratio=0.16; 95% CI: 0.08, 0.35; p<0.001).

**Vamorolone, a dissociative steroid for Duchenne Muscular Dystrophy**

Vamorolone is an oral, selective, dissociative corticosteroid developed for the treatment of patients with muscular dystrophy. Vamorolone was approved in October 2023 for the treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older in the USA and received a positive opinion in the EU in October 2023 for the treatment of DMD in patients 4 years of age and older. Vamorolone is a partial agonist of the glucocorticoid receptor with relative loss of transactivation activities, but retention of transrepression activities, compared to other glucocorticoids. As a result, it is described as possessing "dissociative" glucocorticoid properties. In contrast to other corticosteroids, vamorolone is a potent antagonist of the mineralocorticoid receptor and hence has anti-mineralocorticoid activity.

## Be Cautious…. Drug Safety Alerts

| S. No. | Drug | Safety Alerts |
|---|---|---|
| 1. | Azithromycin | Risk of fatal heart rhythms |
| 2. | Bupropion | Risk of Brugada syndrome |
| 3. | Cefazolin sodium hydrate and cefazolin sodium | Risk of acute coronary syndrome accompanying allergic reaction |
| 4. | Dexibuprofen (oral) | Risk of DRESS syndrome |
| 5. | Finasteride | Risk of suicide-related events |
| 6. | Rivastigmine | Risk of Prolonged QT |

## Clinical Data Management (CDM)

Clinical Data Management (CDM) is an essential component of clinical research, focusing on the collection, storage, and analysis of data generated in clinical trials. It ensures the accuracy, reliability, and integrity of clinical trial data by following standardized procedures and utilizing advanced technology. The term "Clinical Data Management Systems" (CDMS) refers to the software tools (eClinical Suite, RAVE, CLINTRIAL etc.) that are developed specifically for the purpose of clinical data management. The process of CDM includes various stages, such as designing Case Report Forms (CRF), annotating CRFs, designing databases, data entry, data validation, managing discrepancies, medical coding, data extraction, and locking the database.

**Designing Case Report Forms (CRF)**

The CRF should possess a user-friendly interface, concise, and self-explanatory with instructions provided to investigators to facilitate error-free data acquisition.

**Annotating the CRFs**

Annotating CRFs in CDM is the process of linking each data point in the CRF to the corresponding variable name in the database. Annotations are often entered in a distinct color or format to differentiate from the CRF content itself. This is done to facilitate data entry, data management, and query resolution processes.

**Designing database**

Designing a database for CDM is a crucial task that involves creating a structured system to collect, store, and manage data generated from clinical trials. A well-designed database is essential for achieving high-quality data that is reliable, consistent, and suitable for statistical analysis.

**Data entry**

It is the process of transcribing information from paper or electronic case report forms into a clinical trial database. It is a fundamental step for ensuring the accuracy and reliability of the data collected in clinical trials and effective data entry is crucial for producing a high-quality, reliable dataset for clinical trial analysis.

**Data validation**

Data validation refers to the systematic examination of data to ensure its accuracy and compliance with the specified protocol. In order to ensure the data saved in the database is accurate, edit check algorithms are made to discover discrepancies.

**Discrepancy management**

Discrepancies may occur as a result of missing data, inconsistent data and protocol violations. Discrepancy management in CDM refers to the process of identifying, documenting, querying, resolving, and preventing discrepancies in clinical trial data. The integrity of the data from clinical trials requires comprehensive discrepancy management and ensuring it meets the standards needed for regulatory submission and decision making.

**Medical coding**

Medical coding standardizes the terminology for diseases, adverse events, procedures, and medications, which assists in consistent data interpretation and reporting across different clinical trials and sites. Standard codes allow for more efficient and accurate analysis, as data from various sources can be easily compared and aggregated. Coding ensures compliance with international regulations and facilitates the communication of clinical trial data to regulatory agencies in a standardized format. As clinical trials are often international, medical coding enables harmonization of data across different countries and languages.

**Data extraction**

Data extraction is a crucial link between data collection and analysis in clinical trials. It is the process of retrieving specific sets of data from a database for further analysis and reporting. It is a pivotal task that facilitates the transformation of raw data into meaningful information, which can be used for statistical analysis, regulatory submissions, or interim data reviews.

**Database locking before data analysis**

All data management tasks should be done prior to the database lock. To achieve this, a pre-lock checklist is implemented, and all activities are verified. Locking the database and extracting clean data for statistical analysis is done once all stakeholders have given their approval. Database locking before data analysis in CDM is a crucial step to ensure the finality of the clinical trial data.

**The Role of CDM professionals**

Clinical Data Management professionals (Data manager, Database Designer, Medical coder, Clinical Data coordinator, Quality control associate, and Data entry associate) are responsible for generating high-quality data by designing, implementing data collection tools and effectively managing clinical trial data. They also oversee data validation and cleaning processes to identify and resolve any discrepancies or errors. Additionally, they work closely with other stakeholders in the clinical research process, such as investigators, biostatisticians to ensure that the data collected meets regulatory requirements.

In conclusion, effective CDM is crucial for ensuring the integrity, high quality, and reliability of clinical trials. By implementing robust data collection, storage, and analysis processes, it aids in the development of safe and effective treatments. With the ever-growing volume of clinical data, it is essential for data management professionals to stay abreast of technological advancements and regulatory requirements to meet the evolving demands of the pharmaceutical industry. By adhering to best practices and leveraging innovative tools, CDM can continue to advance, ultimately leading to improved patient outcomes.

**Reference:**

Krishnankutty B, Bellary S, Kumar NB, Moodahadu LS. Data management in clinical research: An overview. Indian J Pharmacol. 2012; 44(2):168-72.

## New Drug Approvals…

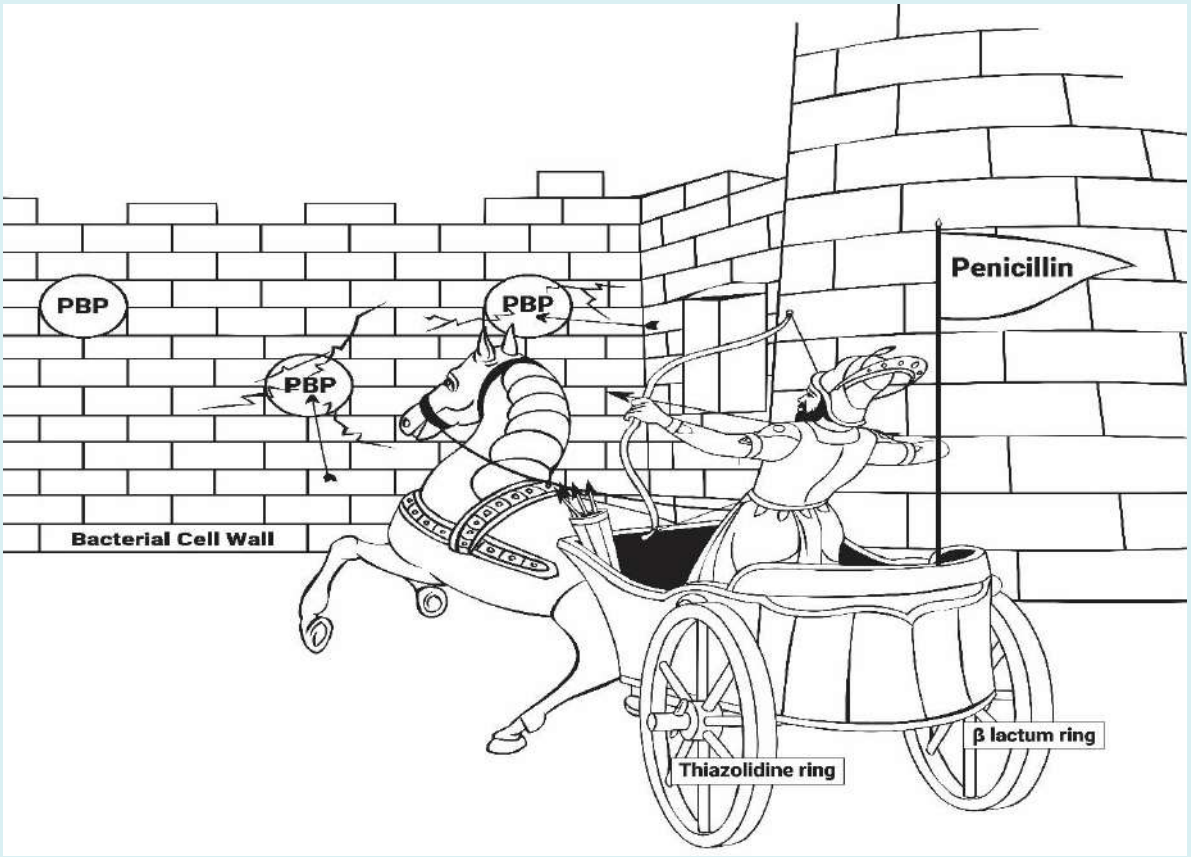
Aprocitentan is an endothelin receptor antagonist approved for the treatment of hypertension in combination with other antihypertensive drugs. The recommended dose is 12.5 mg orally once daily.

Vadadustat is a hypoxia-inducible factor prolyl hydroxylase (HIF PH) inhibitor approved d for the treatment of anemia due to chronic kidney disease (CKD) in adults who have been receiving dialysis for at least three months. The recommended dose is 300 mg orally once daily.

Tislelizumab is a programmed death receptor-1 (PD-1) blocking antibody approved for the treatment of unresectable or metastatic oesophageal squamous cell carcinoma (ESCC) after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor. The recommended dose is 200 mg as an intravenous infusion once every 3 weeks.

Resmetirom is a thyroid hormone receptor-beta (THR-beta) agonist approved for the treatment of noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis. The recommended dose is 80 mg orally once daily if weight is less than 100 kg.

## Cartoon Corner…




Excerpt from "Drug Autobiographies in Pharmacology" by Dr. Sushil Sharma

**Introduction:**

In statistics, nonparametric tests are methods of statistical analysis that do not require a distribution to meet the required assumptions to be analyzed (especially if the data is not normally distributed). Due to this reason, they are sometimes referred to as distribution-free tests. Nonparametric tests serve as an alternative to parametric tests such as T-test or ANOVA that can be employed only if the underlying data satisfies certain criteria and assumptions.

Non-parametric statistical tests offer valuable alternatives to their parametric counterparts, particularly when data do not meet the assumptions required for parametric tests or when dealing with ordinal or non-normally distributed data. These tests provide robustness and flexibility in various research scenarios, offering reliable inference without stringent distributional assumptions. In this discourse, we delve into the essence, applications, and advantages of non-parametric statistical tests of significance.

Non-parametric tests, also known as distribution-free tests, do not rely on assumptions about the underlying population distribution. Instead, they focus on the ranking or ordering of data values. These tests are particularly useful when data violate assumptions of normality, homogeneity of variance, or when dealing with categorical or ordinal data.

**Types of Non-parametric Tests:**

1. Wilcoxon Signed-Rank Test: This test compares paired data samples to assess if their distributions differ significantly. It is a robust alternative to the paired t-test, suitable for non-normally distributed data.
2. Mann-Whitney U Test: Used to compare two independent groups to determine if there is a significant difference between their distributions. It is analogous to the independent samples t-test but applicable to ordinal or non-normally distributed data.
3. Kruskal-Wallis Test: An extension of the Mann-Whitney U test, it compares the median ranks of three or more independent groups to determine if there are significant differences among them.
4. Friedman Test: This non-parametric alternative to the repeated measures ANOVA assesses whether there are significant differences in multiple related groups across different conditions.
5. Spearman's Rank-Order Correlation: Used to assess the strength and direction of association between two variables when the data are ordinal or not normally distributed.

6. Kendall's Tau: Similar to Spearman's correlation, Kendall's Tau measures the strength and direction of association between two variables but is more robust to ties in the data.

**Advantages of Non-parametric Tests:**

1. Robustness: Non-parametric tests are robust to outliers and deviations from normality, making them suitable for analyzing real-world data that may not meet parametric assumptions.
2. Applicability to Ordinal Data: Non-parametric tests can handle ordinal data effectively, preserving the information about the order or ranking of observations.
3. No Assumption of Population Distribution: Unlike parametric tests, non-parametric tests do not assume a specific population distribution, enhancing their applicability to diverse datasets.
4. Simplicity: Many non-parametric tests have straightforward interpretations and are easy to implement, making them accessible to researchers with varying levels of statistical expertise.
5. Wide Range of Applications: Non-parametric tests are versatile and applicable across various fields, including medicine, social sciences, environmental studies, and economics.

**Limitations of Non-parametric Tests:**

1. Less Statistical Power: Non-parametric tests typically have less statistical power compared to their parametric counterparts, especially when data meet parametric assumptions.
2. Loss of Efficiency: Non-parametric tests may lose efficiency when applied to data that conform to parametric assumptions, leading to less precise estimates of effect sizes.
3. Limited to Rank Order: Non-parametric tests focus on rank ordering of data and may not fully utilize the information present in the original data, potentially leading to loss of statistical power.
4. Sample Size Considerations: Some non-parametric tests may require larger sample sizes to achieve the same level of statistical power as parametric tests, particularly in small sample scenarios.

**Practical Considerations:** When deciding whether to use non-parametric tests, researchers should consider the nature of their data, the assumptions of parametric tests, and the specific research question at hand. While non-parametric tests offer robustness and flexibility, they may not always be the most powerful option, especially in scenarios where data meet parametric assumptions.

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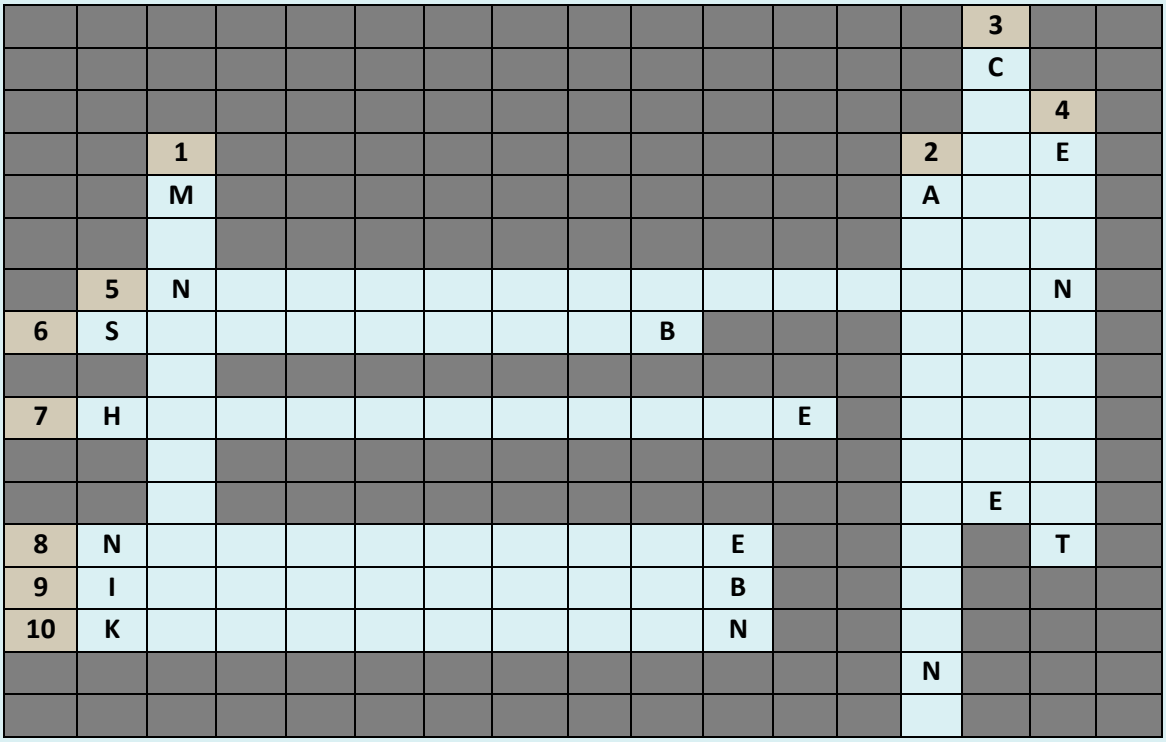


| **Downward** | **Across** |
|---|---|
| 1. Broad spectrum antimicrobial agent acts by inhibition of protein synthesis (*11*)<br>2. Hypolipidemic drug acts by inhibition of rate limiting step of cholesterol synthesis (*12*)<br>3. Third generation parenteral cephalosporin (*11*)<br>4. TNF-α Inhibitor (*10*) | 5. Urinary antiseptic (*14*)<br>6. Oral multikinase inhibitor used against cancers *(9)*<br>7. Direct vasodilator used in treatment of essential hypertension *(11)*<br>8. NSAID with preferential COX-2 selectivity *(10)*<br>9. Monoclonal antibody which targets TNF -α *(10)*<br>10. NSAID with Propionic acid derivative *(10)* |

**Answer to the Crossword Puzzle is given below:**

**Downward**

1. Minocycline 2. Atorvastatin 3. Ceftriaxone 4. Etanercept 5. Nitrofurantoin 8. Nimesulide

**Across**

6. Sorafenib 7. Hydralazine 9. Infliximab 10. Ketoprofen