DRUG TARGETS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

Education

Presentations

Rheumatoid arthritis (RA) is a chronic inflammatory disorder with an estimated prevalence of 0.5-1% of the population worldwide; it is also reported that women are more affected than men are. [1]. RA is characterized by joint inflammation,
synovial proliferation and destruction of articular cartilage. Immune complexes composed of IgM activate complement and release cytokines (mainly TNF**α** and IL-1) which are chemotactic for neutrophils. These inflammatory cells secrete lysosomal enzymes, which damage cartilage and erode bone, while PGs produced in the process cause vasodilatation and pain.

INTRODUCTION

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INTRODUCTION

Anti-rheumatoid drugs are the drugs which (except corticosteroids), can suppress the rheumatoid process, bring about remission and retard disease progression, but do not have nonspecific anti-inflammatory or analgesic action. They are used in RA in addition to NSAIDs and are referred to as disease-modifying anti-rheumatic drugs (DMARDs).

The goals of drug therapy in RA are:

- Ameliorate pain, swelling and joint stiffness
- Prevent articular cartilage damage and bony erosions
- Prevent deformity and preserve joint function

TREATMENT STRATEGIES

Development of the treatment strategies for RA has significantly improved outcomes for patients with RA. Presently, the anti-rheumatoid drugs are mainly divided into five classes:

1. Analgesics
2. Non-steroidal anti-inflammatories (NSAIDs)
3. Glucocorticoids
4. Biologic disease-modifying anti-rheumatic drugs (DMARDs).
5. Non-biologic DMARDs

TREATMENT STRATEGIES

1. **Analgesics & NSAIDs:** In RA treatment, analgesics are used mainly on temporary basis or for acute cases. Among the various analgesics, acetaminophen (paracetamol) is the most commonly used analgesic due to its minimal side effects. The primary outcome of NSAIDs is to inhibit cyclooxygenase (COX) 1 and 2, and inhibit the conversion of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. However, due to their cardiovascular and gastrointestinal side effects, several marketed NSAIDs were withdrawn from the market.

TREATMENT STRATEGIES

2. **Glucocorticoids:** To reduce the disease activity in chronic RA, glucocorticoids are frequently included in the RA treatment regimen. Short-acting glucocorticoids such as prednisolone can be administered orally or parenterally long-acting glucocorticoids, such as methylprednisolone 80–120 mg or triamcinolone 80 mg can be given intramuscularly and when required for disease flares.

TREATMENT STRATEGIES

3. **Biological DMARDs:** Various biological DMARDs are the tumour necrosis factor (TNF) alpha inhibitors, anti-B cell therapy, T-cell co-stimulation blocker, anti-Interleukin 6 (IL-6), anti-Interleukin 1 (IL-1), and protein kinase inhibitors. Beside the efficacy and side effects, other factors may also influence the selection of a drug for patient such as dosing, route of administration, cost and national guidelines. There are standardized guidelines for the nomenclature of these biologic drugs: all the receptors are ends with "cept"; if the drug ends with "mab," "zumab," "mumab," or "inib" it suggests chimeric monoclonal antibody, humanized monoclonal antibody, fully human monoclonal antibody, or small molecule kinase inhibitors, respectively.

TREATMENT STRATEGIES

4. **Non-biological DMARDs:** Oral DMARDs, the mainstay of rheumatoid arthritis treatment, were the first drugs available that affect the immune system. But over the past 15 years, a multitude of new biologic therapies have hit the market, which targets particular cells of the immune system. New small molecules are also in development that aims intracellular immune signalling. The first breakthrough in rheumatoid arthritis treatment was methotrexate. Since then, numerous biologics have been approved. The first biosimilar was approved in 2013, introducing more price competition to the biologics market (Figure 1).

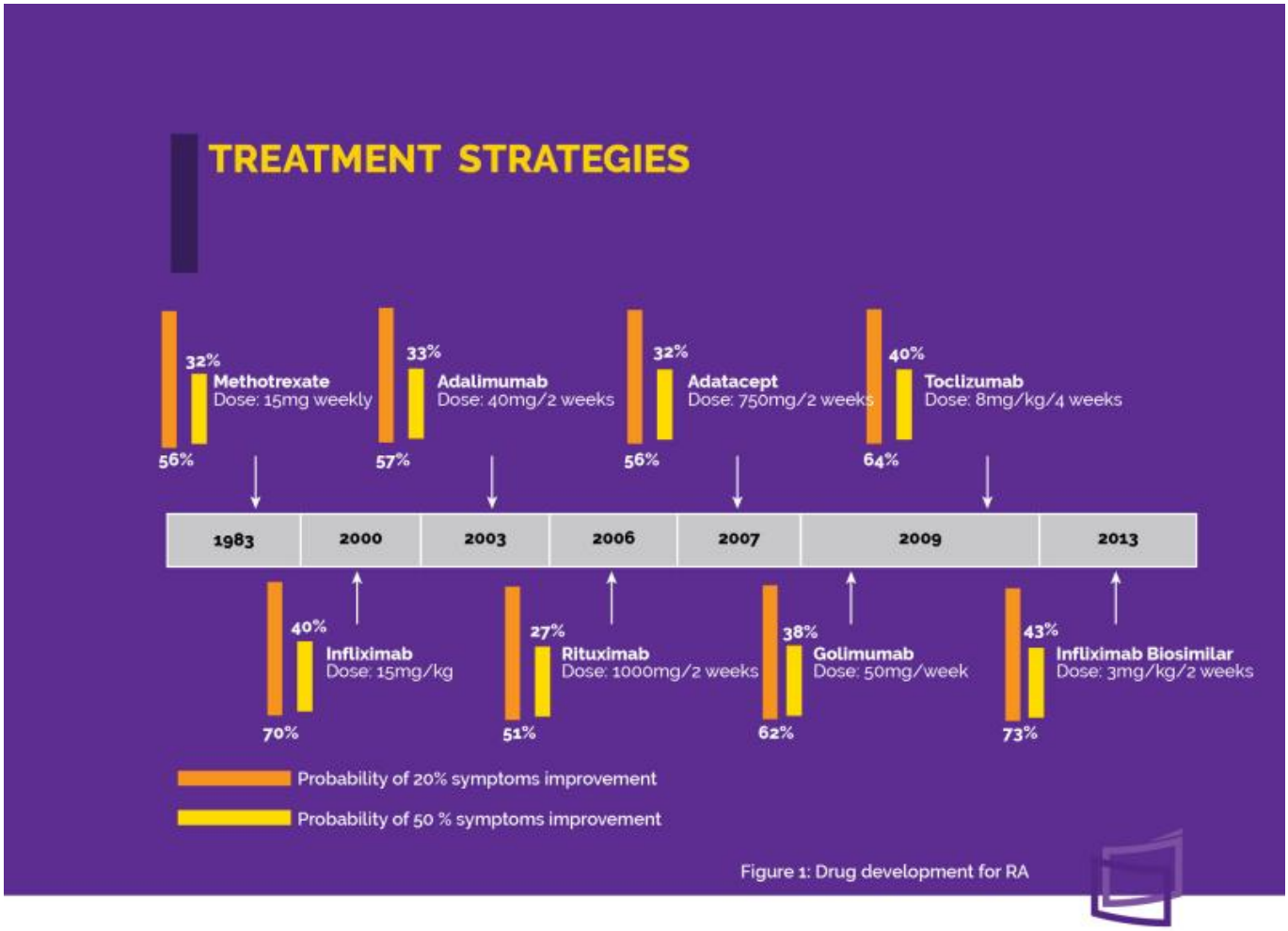
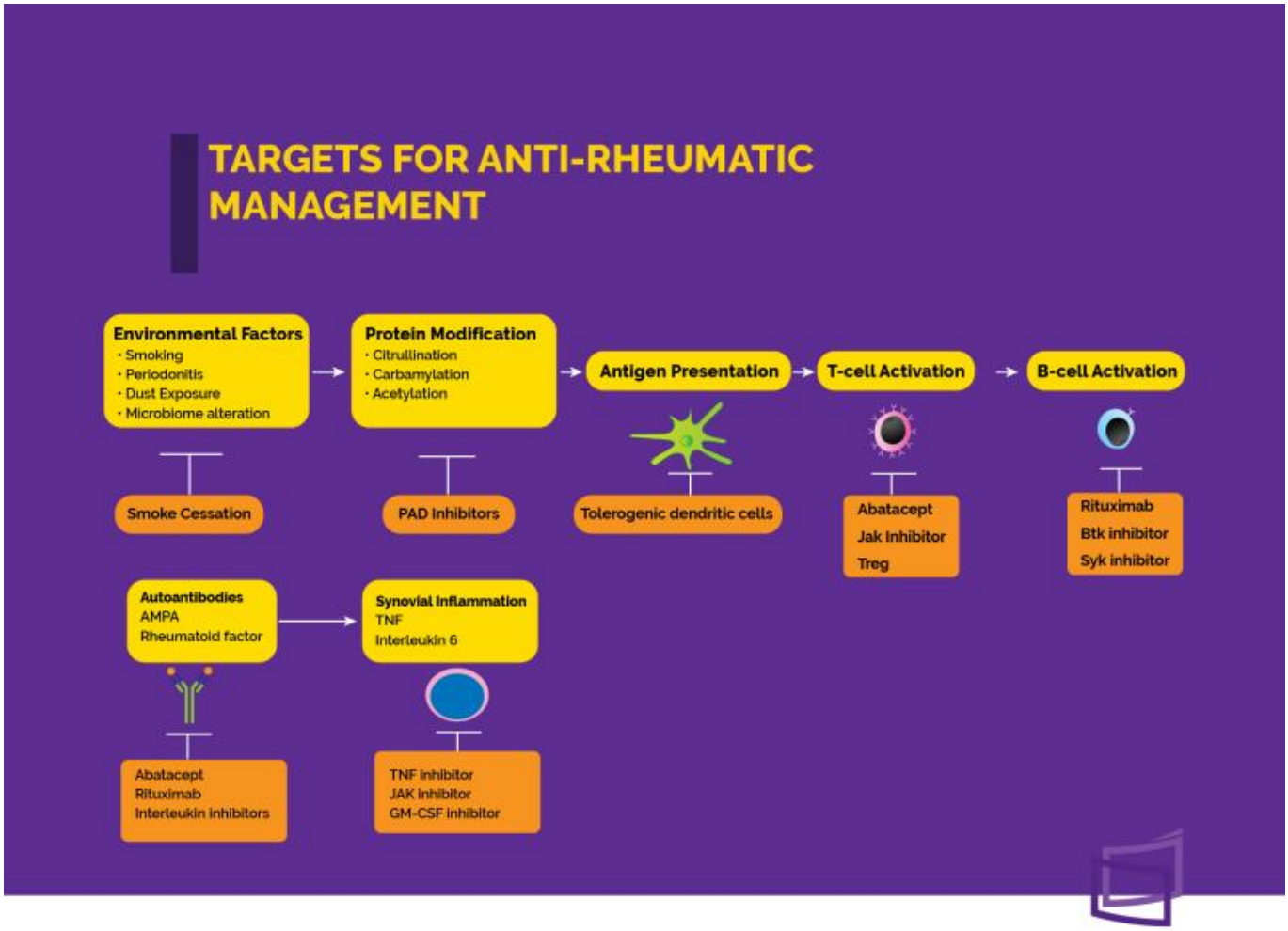


Figure 1: Drug development for RA

TARGETS FOR ANTI-RHEUMATIC MANAGEMENT

- **Various targets of anti-rheumatoid drugs:** With the advancement in the technology, it is now possible to target specific elements in the immune system which are responsible for the generation of RA (e.g., cytokines, B-cells, antigen presenting cells (APCs), and T cells). The present article has given an update on different features of the pharmacotherapeutic interventions in RA [3].


TARGETS FOR ANTI-RHEUMATIC MANAGEMENT
Environmental Factors
· Smoking
· Periodonitis
· Dust Exposure
· Microbiome alteration
Smoke Cessation
Protein Modification
· Citrullination
· Carbamylation
· Acetylation
PAD Inhibitors
Antigen Presentation
Tolerogenic dendritic cells
T-cell Activation
Abatacept
Jak Inhibitor
Treg
B-cell Activation
Rituximab
Btk inhibitor
Syk inhibitor
Autoantibodies
AMPA
Rheumatoid factor
Abatacept
Rituximab
Interleukin inhibitors
Synovial Inflammation
TNF
Interleukin 6
TNF inhibitor
JAK inhibitor
GM-CSF inhibitor

CONCLUSION

With the advancement in the medical sciences in the last two decades, a number of drugs are available for the management of RA. Both the biological and non-biological DMARDs have significantly relieved patients from RA and must be started as early as possible. However, it is still unclear that which biologics in what order should be used as it depends on various factors such as cost and route of administration. Currently, anti-TNF is the commonly used first-line biologic worldwide, followed by abatacept in combination with MTX. Due to the safety concern, rituximab is not generally used as a first line biologic therapy but is still as active as anti-TNF. Monoclonal antibodies seem to produce more immunogenicity than other types of biologics.

REFERENCES

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2. Tripathi KD. Essentials of medical pharmacology. JP Medical Ltd; 2013 Sep 30.
3. Clin Med Insights Arthritis Musculoskelet Disord. 2013; 6: 35–43

Therapeutiv, NSAIDs, Rheumatoid arthritis, Drug targets