Asthma and Arthritis: Are there any similarities?

Asthma
Asthma is a serious global health problem that is broadly distributed by age, sex, race/ethnicity, and geographic location. International statistics indicate that asthma prevalence, morbidity, and mortality have increased significantly since the early 1970s. Whereas some studies indicate continued increases through the mid 1990s, others show recent downward trends, especially in asthma hospitalizations and mortality. Among possible contributors to the observed trends are patterns of drug therapy.

Therefore it would seem that patient outcomes in asthma depend strongly on appropriate medication use. Traditionally, symptomatic relief of bronchospasm with short-acting β2 agonists was the mainstay of therapy. Numerous studies, however, suggest that this therapy alone is ineffective and that regular use of β2 agonists might actually increase the risk of morbidity and mortality. Not until the early 1990s was inflammation widely recognized as the predominant cause of reversible airway obstruction and airway hyper-reactivity. As a result, treatment has shifted to the early and regular use of anti-inflammatory “controller” medications (especially inhaled corticosteroids) for control of airway inflammation. Short-acting β2 agonists and other “reliever” medications are now recommended for as-needed use for relief of acute bronchoconstriction. Appropriate use of inhaled corticosteroids is associated with improved patient outcomes. Many studies in the last decade, however, suggested underprescription and underutilization of inhaled corticosteroids.

Therefore, chronic inflammatory diseases such as asthma, and the changing treatment paradigms have proven to be a classic case study of metamorphosis. Evolving from treating asthma initially with β2 stimulants and using corticosteroids only during exacerbations, to present day current asthma guidelines that advocate corticosteroids therapy early followed by β2 stimulants (“hit early, hit hard”).

Rheumatoid arthritis
Rheumatoid arthritis (RA) is also a chronic systemic inflammatory condition that affects approximately 0.8% of the population worldwide. Women are affected 3 times as often as men, and the peak incidence occurs between 40 and 60 years, but all ages can be affected.

RA is characterized by synovitis within diarthrodial joints. Angiogenesis is an important early event. Among the numerous cell types present within the inflamed joint, CD4 helper T cells appear to play a key role in orchestrating the immune response. Activation of T cells occurs more efficiently in an inflammatory milieu, suggesting interplay between the innate and specific immune systems. Activated macrophages are an important source of inflammatory factors, including key proinflammatory cytokines, such as tumor necrosis factor (TNF-α) and interleukin 1 (IL-1). Among their many activities, TNF and IL-1 promote accumulation of inflammatory cells and the synthesis of other cytokines, chemokines, matrix metalloproteinases, and other inflammatory mediators. B cells contribute to the ongoing inflammation by activating T cells and producing potentially pathogenic autoantibodies: rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP).

The primary goals of therapy for RA are relief of pain, reduction of inflammation, preservation of functional status, prevention of disease and therapy complications, and resolution of the pathogenic process. Historically, RA had been viewed as a benign disease, and it was managed conservatively, starting with nonsteroidal anti-inflammatory drugs (NSAIDs). However, it is now established that RA is an aggressive disease associated with substantial morbidity and accelerated mortality. Subsequently, the treatment has become more aggressive, with earlier institution of treatment with disease-modifying antirheumatic drugs and TNF-α inhibitors (etanercept, infliximab, and adalimumab). Commonly used disease modifying antirheumatic drugs (DMARD) include methotrexate, hydroxychloroquine (HCQ), sulfasalazine, and leflunomide.

The link
A possible link between asthma and arthritis has been alluded to by a distinct lineage of CD4 T helper cells that regulate tissue inflammation by producing interleukin 17 (IL-17). IL-17 (also called IL-17A) has been associated with many inflammatory diseases such as rheumatoid arthritis and asthma. These diseases are characterised by an immune response in which TNF-α is generated in excess.

The IL-17 receptor is distributed ubiquitously in various tissues, and studies conducted on IL-17 receptor deficient mice have shown impaired host defense against microbacterial infection because of a substantial reduction in granulocyte colony-stimulating factor and macrophage inflammatory protein 2 in the lung. IL-17 is also important in contact, delayed-type hypersensitivities, as shown in a study using IL-17 deficient mice. In related reports, IL-17 deficient, as well as wild-type mice receiving an IL-17 receptor antagonist, have shown resistance to an arthritis-like disease.

Treatment with monoclonal antibodies
The introduction of biological treatments such as the afore-mentioned TNF-α antagonists brings new hope and new treatment options to patients with RA. The use of biological treatments is now widespread, and, to date, approximately 1 million patients in the world have been treated...
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chronic, unresolved inflammation is a structural change in the airway, termed airway remodeling\(^5\). An interesting therapeutic strategy is the use of the anti-IgE monoclonal antibody, omalizumab, which is used in asthma, and trials are in progress in food allergies, eczema and severe resistant rhinitis.

With TNF-\(\alpha\) antagonists, key safety considerations include (1) infection, both common and opportunistic, (2) cytopenias, (3) demyelinating disease, (4) lupus-like syndromes, (5) congestive heart failure, and (6) malignancies, particularly lymphomas. For the most part, serious adverse events are uncommon and the risks appear manageable. Despite the risks inherent in therapy with TNF-\(\alpha\) antagonists, the risk/benefit ratio to date is extremely good. However, only prolonged observational studies will address issues long-term regarding the frequency of known adverse events, as well as early ascertainment of rare events\(^10\).

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treated with TNF-\(\alpha\) antagonists. However, large-scale immunotherapy has requirements of which one should be aware. It is essential that users acquire a very high level of qualification. For handling biological therapeutics well, it is necessary to know the characteristics of biological tools (monoclonal antibodies, soluble receptors); in particular, their mode of action and their pharmacokinetic and pharmacodynamic properties\(^8\).

To optimise the use of these molecules, it is essential to know not only their characteristics but also the individual factors which make it possible to predict effectiveness and tolerance. Various approaches will allow a true ‘pharmacoprediction’ in order to determine ‘the right drug for the right patient’. Thus, if this objective is achieved, it might be possible, in the immediate future, to propose à la carte therapeutic strategies, which avoid the most severe effects associated with the successive use of empirical immunosuppressor treatments.

Today, there are four types of well-defined monoclonal antibody nomenclature: the suffix ‘mab’ of the international common denomination is preceded by a prefix determined by the origin of the antibody, ‘mo’ for murine (muromonab), ‘xi’ for chimeric (rituximab), ‘zu’ for humanised (trastuzumab) and ‘mu’ for completely human (adalimumab). The use of murine monoclonal antibodies in man has associated risks because of the very strong immunogenicity possibility. This led to the development of nonmurine monoclonal antibodies, initially chimeric ones, then came humanised ones: and finally, entirely human monoclonal antibodies were developed\(^9\).

The most recent TNF-\(\alpha\) antagonist to be introduced into the market, adalimumab given as monotherapy provides significant effectiveness and improvement in the Health Assessment Questionnaire disability index (HAQ DI) and there is improvement in health utility scores for patients with RA who are not responsive to DMARDs. In addition, a cost-effectiveness analysis suggests that adalimumab is more cost effective than infliximab and at least as cost-effective as etanercept\(^10\). A recent study has shown that in patients with early, aggressive RA, combination therapy with adalimumab plus methotrexate (MTX) was significantly superior to either MTX alone or adalimumab alone in improving signs and symptoms of disease, inhibiting radiographic progression, and effecting clinical remission\(^7\).

Researchers have also addressed the potential role of TNF-\(\alpha\) in asthma and have put forward the idea that drugs which have been developed to neutralize the deleterious effects of TNF-\(\alpha\) may also be useful in the management of chronic severe asthma\(^8\). This is because extensive genetic, biologic, and physiological evidence indicates that TNF-\(\alpha\) plays a critical role in the initiation and amplification of airway inflammation in patients with asthma. Preformed TNF-\(\alpha\) is stored by mast cells and rapidly released during IgE-mediated reactions that typify the asthmatic response to allergens. TNF-\(\alpha\) perpetuates and amplifies inflammation by up-regulating adhesion molecules, which leads to increased migration of eosinophils and neutrophils into the airways. These key effector cells, as well as resident structural cells such as airway epithelial cells, are activated by TNF-\(\alpha\) to release cytotoxic mediators and reactive nitrogen and oxygen species that result in airway injury. The end result of