Each type of cause that initiates Rheumatoid Arthritis or RA flares differentially affects the response to therapy.

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Abstract

The autoimmune disease rheumatoid arthritis (RA) presents difficulty in diagnosis, commonly observed flare ups, polycyclical nature of RA progression, and variable response to therapies. Congruent with multiple causes, literature has documented various infectious agents, environmental factors, physical trauma, silica and food sensitivities as potential causes of RA or RA flares in different populations. We propose that these >36 events can initiate RA or RA flares which complicates treatment decisions. Each pharmaceutical medicine benefits 15% - 82% of RA patients. Predictive factors are needed. Because the initiating cause of RA or RA flare affects the type of joint damage, initial inflammatory response, adaptive immune response, and potential molecular mimicry, we propose the “RA cause affects response to therapy” (RACART) theory. The potential cause combined with confounding factors such as genetic risk factors, nutritional status, epigenetic status, inflammatory levels, and detoxification ability may help predict responses to various therapies.

Introduction

Characteristics of the autoimmune disease Rheumatoid arthritis (RA) include persistent symmetrical swelling and tenderness of multiple joints, morning stiffness, elevated acute phase markers, and often autoantibodies, subcutaneous nodules, and erosive destruction of the joint spaces (1). RA is also plagued with difficulty in diagnosis, commonly observed flare ups of symptoms, polycyclic nature of progression, and wide variation in response to therapies. A flare is defined as “any worsening of disease activity that would, if persistent, in most cases lead to initiation or change of therapy” (2). Increased disease activity and uncontrolled flares are associated with joint damage and a loss of fat-free mass (3). A prolonged flare is associated with the tendency towards cachexia (3). Because RA flares indicate a worsening of inflammation in the joints, management of RA flares can improve symptoms and may delay disease progression. Clinical practice still involves “trial and error” in daily treatment decisions (4) due to unpredictable responses to therapy in a given patient. Managing a flare often involves addition of a therapy that is new to that patient, a boost in the dosage of a current therapy, and/or the addition of non-steroidal anti-inflammatory drugs (NSAIDs) (5).

The goals of patient-tailored medicine include optimizing treatment efficacy, minimizing risk of toxicity from ineffective therapeutic agents, and minimizing costs (4). Most medications and supplements exhibit an efficacy of 15%-82% in RA patients (4, 6-9). Each class of medication provides a specific mode of action to thwart the RA symptoms or modulate the inflammatory and immune responses in RA patients. Medications in a class exhibit overlapping mechanisms of action; their side effects often are related to their mechanisms of action. Identification of genetic markers predictive of the response to a given pharmaceutical drug is being pursued, but no genetic markers are sufficient predictors for clinical use (4). Distinct biomarker profiles derived

from proteomic, autoantigen, and cytokine analyses have provided predictive insights but require further studies (4).

As an alternative strategy, identification of the patients' cause of RA or cause of a recent RA flare may improve the subsequent choice of medication. Although no single potential cause explains the presence of symptoms in all rheumatoid arthritis patients (4, 10), most rheumatologists and scientists agree that the etiology of RA is multifactorial and involves interactions of genetic susceptibilities, environmental agents, nutritional status, exercise, and detoxification ability (4, 10). For example, the shared epitope in the HLA-DRB1/DR4 alleles increases the risk of RA in multiple ethnic populations (11) and appears to modulate the risk of several environmental agents (12). Other polymorphisms such as GST^{null} (13), PTPN22 (14), CTLA4, and STAT can increase the risk of RA in some ethnic populations (15), but not others (11). However, monozygotic twin studies show that genotype alone does not guarantee the initiation and progression of RA (16). Thus, one or more initiating events must trigger a cascade of inflammatory responses that do not resolve the triggering event in some people. The outcome of these induced inflammatory responses is dependent on the epigenetic profile of numerous genes involved in the T cell, B cell, mast cell, dendritic cell, pro-inflammatory, and regulatory responses (17). Various factors including nutritional status, genetic risk factors, previous infectious history, exercise intensity, and detoxification ability can modulate expression of the pro-inflammatory and destructive mediators via epigenetic processes (17).

Numerous pathogens, environmental toxins, silica, trauma, and food sensitivities have been reported to be associated with the onset of RA in various populations. Many of these agents or events may also affect the polycyclic nature of RA progression by contributing to the development of RA flares, although etiology of flares is less well studied and remains elusive.

Hypothesis

We agree that the initial cause of rheumatoid arthritis is multifactorial and the initiating episode can involve one or more distinct events in subpopulations of patients (4, 10). Similarly, the cause of RA flares is multifactorial and likely involves interactions of environmental agents (pathogens, environmental toxins, silica, physical trauma, and food sensitivities), genetic susceptibilities, nutritional status, inactivity, overexertion, mental outlook, and detoxification ability. We also acknowledge that response to therapies vary greatly in different RA patients, in agreement (4). We propose that these therapeutic responses are congruent with the distinct mechanisms of action for each medication or herbal supplement and the patients' need for that modulation. We propose that (i) the initiating cause of RA or a subsequent RA flare can affect the type of joint damage, inflammatory response, adaptive immune response, and development of molecular mimicry and that (ii) the patient's response to therapy depends on the initiating cause(s) of their RA symptoms or the immediate RA flare as well as the mechanism of action of the medication or therapy, genetic risk factors, nutritional status, physical routine, and detoxification ability. In short, this theory has been named the "RACART" theory as an acronym for RA cause affects response to therapy.

Evaluation of the hypothesis

Evidence for multiple types of initiating events

Various factors and events have been proposed as the cause of RA in a specific population of RA patients (10). Each potential cause of Rheumatoid Arthritis may induce symptoms in a subset of the RA patient population. First, physical trauma was reported to be a precipitating

event in approx. 21% of RA patients (18). Smolen et al have proposed that active joint damage can elicit further joint inflammation in a downward spiral of RA disease progression (19).

Second, Dr. Leirisalo-Repo concluded that approximately 20% of rheumatoid arthritis patients had an infection preceding their disease (20). Infections with the bacteria, *Proteus (21)*, mycoplasma (*Mycoplasma arthritidis, Mycoplasma fermentans, Mycoplasma pneumoniae, M. hominis, and M. salivarium*), *Chlamidia trachomatis (22)*, *Porphyromonas gingivalis (23), actinobacteria* (24), *Escherichia coli*, the viruses (20) such as Epstein Bar Virus (25), Cytomegalovirus (CMV) (26), Herpes Simplex virus types I and II (27), Parvovirus B-19, and the molds (24) such as *Petriellidium boydii*, and *Candida albicans* have been implicated as a trigger for RA in various subpopulations. Specific genotypes (single nucleotide polymorphisms (SNPs) in TNF-238 A, lymphotoxin alpha +365 C, FCGR3A 176F) significantly increase the risk of urinary tract infections in a dose-dependent manner in early RA (28). In addition, unusual infections such as *Legionella* may trigger a “RA flare” (29). Removal of root canal revealed a pus layer; after removal, patient experienced remission for ≥ 16 yrs (30). The CD64 activation marker on neutrophils has significantly correlated with infections involving bacteria, fungi, mycoplasma, and viruses in RA patients, regardless of the patients’ concurrent medication (31). Taken together, these data support the role of bacteria, viruses, and molds in the etiology of RA and in the triggering of a RA flare in some RA patients.

Third, mast cells are significantly elevated in afflicted RA synovial spaces (32). Historical data have documented that food sensitivities may trigger or exacerbate RA symptoms in 5% to 30% of patients, depending on the foods absent in the diet in a given study (33-35). Twenty common foods that exacerbated RA in some patients were identified (36). Approximately one third of RA patients resolved their RA symptoms for 7.5 years by solely adhering to a personalized diet (37). Coffee was reported to be the tenth most common food sensitivity in RA patients (36). Heavy coffee drinkers (≥5 cups) who had the DR4/1 shared epitope genotype had a significantly increased risk of developing RA (OR: 53.3) in one study (12) but not another study (38). Decaffeinated coffee increased the risk more than caffeinated coffee in a study (39). In contrast, heavy green tea drinkers were significantly protected against development of RA (OR: 0.24) in one (39) but not another study (38). These data support the recent reports of mast cells playing a significant role in inflammatory events in RA-afflicted joints (40). For example, mast cells are a major source of IL-17A in RA-afflicted joints (40). IL-17 contributes to bone destruction, remodeling, and excessive angiogenesis involved in pannus formation (41, 42).

Since infection, physical trauma, and food sensitivities only account for approx. 46% of RA cases, other events must also initiate sufficient joint damage, elicit inflammation, and lead to RA diagnosis and / or trigger a flare. Repeated exposures to silica (43), air pollution (44), smoking (12, 45), and pesticides (46) increase the risk of developing RA or triggering a RA flare in a subpopulation (10, 43, 47). Interestingly, individuals who had the HLA DR4 shared epitope and smoked heavily greatly increased their risk of RA (OR: 52.6) (12). However, the percentages of patients with these potential etiologies have not been reported. In addition, exposure to cold may induce an RA flare by eliciting high IL-6 levels (48).

Each of these potential causes or initiating events induces a characteristic inflammatory response for resolution of the damage. In some cases, the initiating event may lead to molecular mimicry wherein the responding cells possess sufficient reactivity to the joint tissue to lead to its inflammation and destruction. The individuals' genotype may affect their ability to resolve the initiating inflammatory event.

Effect of potential cause on inflammatory and immune responses in joint

The inflammatory and immune responses directed towards healing from an infection, physical trauma, food sensitivities, exposure to environmental particulates (air pollution, pesticides) and toxins, and silica theoretically would differ in the strength, breadth, dominant cell types (T cells, B cells, mast cells, monocytes, dendritic cells, neutrophils, regulatory T cells), and duration of the responses (Table 1). Other factors of the patients' overall health such as genotype, current epigenetic profile of regulatory T cells and inflammatory pathways, chronic dehydration, insufficient exercise, nutritional status, and expectation may also influence the outcome.

For example, physical trauma would expose new antigens (23) to the immune response (Table 1). Naive T cells with low affinity for a newly exposed joint antigen may expand and lead to a persistent response (49). A nutritional status with sufficient levels of the 20 essential nutrients in the appropriate proportions supports more rapid healing than a status with low levels of one or more essential bone nutrients (50). Agents that slow the healing of bone fractures would theoretically lengthen the duration of exposure of the immune cells to new joint antigens. Smokers exhibit a prolonged healing of bone fractures (51) which may contribute to the higher risk for developing RA (45), especially in patients carrying the DR4/1 shared epitope (12). Secondly, NSAID usage for pain reduction during repair of bone fractures appears to delay

healing and reduce strength (52, 53). Corticosteroids may also delay fracture healing (50). According to the RACART hypothesis, immunosuppressive agents that do not delay healing of bone fractures may be more likely to reduce flare up due to physical trauma as their initiating event than flares triggered by an infection. For example, TNF in the synovial fluid appears to augment apoptosis of chondrocytes, promote chondroclasts, and delay healing of bone fractures in mice with diabetes (54). Anti-TNF treatment improved healing of bone fractures (54).

Secondly, the class of pathogen affects the type of innate and immune response triggered. The role and potential mechanisms of infectious agents in triggering autoimmune diseases have been reviewed (55). Th1 cells play major roles in resolving infections of intracellular pathogens whereas Th2 cells and Th17 cells are predominant in the responses to extracellular pathogens. Th17 cells play major roles in resolving infections from extracellular organisms including *Staphlococcus aureus, Klebsiella, Borrelia burgdorferi, Candida albicans, and Aspergillus* (56), although Th17 cells also contribute to development of RA pathology (56, 57). Several pathogens contain epitopes that may mimic normal joint tissue (21, 27). For example, the *Proteus* hemoslyn and urease sequences contain sequences similar to the HLA shared epitope region and collagen IX, respectively (21). Secondly, T cell lines specific for Herpes simplex virus type I and *Campylobacter jejuni* displayed an enhanced migratory response towards a synovial-tissue-derived chemokine conditioned media than did the T cell lines specific for *Acanthamoeba polyphaga* (27). A higher frequency of CD8 T cells specific for a tetramer of HLA-A2 complexed to the NLVPMVATV epitope from the CMV pp65 protein were found in synovial fluid compared to that in peripheral blood in all four RA donors (26). These results support the role of Proteus, CMV, and / or HSV infection or reactivation in the onset of RA flares in some RA patients. The PTPN22 1858T allele is a risk factor for rheumatoid arthritis.

Activated T cells with this missense mutation produce less IL-2 and downregulate T cell activation more efficiently than those with the normal PTPN22 1858C allele (14). Whether this PTPN22 1848T allele hinders resolution of all causes of RA flares equally or alternatively whether its reduced immune response may preferentially hinder resolution of infections requires further study. An ongoing tuberculosis infection is a contraindication for some classes of immunosuppressants, such as TNF inhibitors (58).

Third, increased intestinal permeability is prevalent in RA and Juvenile inflammatory arthritis (JIA) patients (59, 60). A major risk factor for increased intestinal permeability is the use of NSAIDs (59). Increased intestinal permeability can allow the transport of incompletely digested proteins into the blood (61), can lead to the breakdown of oral tolerance, and promote the development of food allergies or food sensitivities in genetically susceptible individuals (61). Mast cells, a hallmark of allergies, are significantly elevated in RA-afflicted joints (32) and a major source of IL-17A (40). IL-17 contributes to bone destruction, remodeling, and excess angiogenesis involved in pannus formation (41, 42). Furthermore, RA synovial fibroblasts secrete excess IL-33 which can trigger mast cells to produce pro-inflammatory cytokines and degranulate in the presence of autoantibody (62). Manipulation of the IL-33 receptor in animal models demonstrated a major role of mast cells in arthritis (63). Similarly, silencing of mast cells in an arthritis model protected against joint destruction and angiogenesis (64). Placebo-controlled studies of specific diets indicated that food sensitivities may trigger or exacerbate RA symptoms in 5% to 30% of patients, depending on the foods absent in the diet (33-35). Grains, meats, dairy, and citrus were among the top ten common foods that exacerbated RA symptoms in some RA patients (36). Although the placebo effect existed, the resolution of all RA symptoms in approximately one third of RA patients for 7.5 years by adherence to a personalized diet indicated that food sensitivities play a role in disease manifestation of some

RA patients (37). Anti-TNF therapies reduce the expression of the IL-33 receptor, ST2, on neutrophils (65), but their effects on ST2 expression of mast cells is unknown.

Fourth, environmental toxins such as air pollution, volatile chemicals, pesticides, herbicides, and formaldehyde place a high burden on the detoxification ability of humans. Glutathione plays a major role in the removal of toxins from cells. The GST^{null} allele increases the risk of RA (13, 45) and Juvenile Inflammatory arthritis (JIA), especially systemic JIA (66). Serum levels of dioxin-like polychlorinated biphenols (PCBs) or nondioxin-like PCBs were associated with a significantly higher risk of development of RA in women (47) although mixing and applying pesticides did not correlate with higher risk of RA (67). Substantial air pollution also has increased the risk for onset of RA and Juvenile inflammatory arthritis (44, 68). Smoking, a personal source of air pollution, increases the risk of RA, especially in individuals carrying the HLA DR4 shared epitope (12, 69) and appears to increase the production of anti-cyclic citrullinated protein antibodies (69). Furthermore, the GST^{null} allele was significantly associated with high RA disease activity, especially in smokers (70). Further studies are needed to investigate whether promoting and supporting glutathione production in RA patients can augment the removal of environmental toxins and calm RA flares in most patients. Regardless, reducing the exposure to environmental toxins, such as air pollution, reduces the risk of RA onset (44), and it may help stabilize or improve disease management.

Confounding factors

Genetic influences:

The HLA DR4/1 shared epitope is associated with the risk for development of RA in multiple ethnic populations. As a region in an immune response gene, the HLA DR4/1 shared epitope

augments the risk of smoking in RA onset (12). Genome-wide association studies have used linkage of single nucleotide polymorphisms with RA diagnosis to identify and confirm association with the genes, IL-21, PTPN22, CTLA4, STAT4, CD40, IL6ST, SPRED2, RBPJ, CCR6, IRF5, AFF3, IL-2RA, CCL-21 and PXK (15, 71). Four of these genes, CD244, PADI4, SLC22A2, PTPN22, were overexpressed in RA patients whereas STAT4 was downregulated in RA patients compared to controls (72). In an analogous manner, 7 specific genes or their allelic polymorphisms appear to modulate the response to anti-TNF therapy (8).

Lifestyle choices

Nutritional status also appears to affect the response to therapy. For example, ingestion of 4.5g of omega 3 oils daily with concurrent methotrexate therapy increased the rate of disease remission from 31% to 72% (7). In addition, higher antioxidant levels offered some protection against the development of RA (73), and may function by neutralizing the toxins from the environment or infectious agents. Vitamin C and retinol concentrations were inversely associated with RA disease activity (74).

The human gut normally is colonized by over 400 bacterial species. Some strains of gut flora appear to be more arthritogenic than other strains (75). Intestinal flora, including lactobacilli and bacilli that can modulate the immune response, were associated with reduced disease activity (76, 77).

Exercise induces a mechanical stress on chondrocytes. Low intensity mechanical stress suppresses transcription of IL-1 beta, TNF alpha, and multiple proinflammatory mediators (78). It also increases synthesis of proteoglycans and collagen and suppresses inflammation (78). In contrast, intense mechanical stress or exercise inhibits matrix synthesis, promotes cartilage

destruction (78), induces angiogenesis (79), and is proinflammatory (78). These mechanistic studies (78, 79) help explain the benefits of mild exercise such as Tai Chi, Yoga, walking, and swimming for RA and JIA patients (80). Interestingly, studies suggest that mechanical stress may exert cellular signals that are 2-10 fold stronger than most chemical mediators, including individual cytokines and chemokines (78, 79, 81).

Effects of Hormones

Hormonal status influences the risk of developing rheumatoid arthritis as rheumatoid arthritis occurs in approximately three times as many females as males. However, the mechanisms have not been fully elucidated. Hormonal influences such as prolactin which increase during breastfeeding are associated with an increased risk of flare, relapse of RA, or onset of RA (82). Although the endogenous production of glucocorticords is an important mechanism for regulating the inflammatory processes and can reduce the overall disease activity, the adrenal glands of RA patients may not respond to stress with sufficient production of hormones (83). In addition to its negative effects, acute stress in rats has changed their susceptibility to an autoimmune disease to resistance for multiple weeks (84).

Epigenetic modifications

Activity of a specific gene is influenced by its primary amino acid sequence (polymorphisms), its expression which involves its transcription level, preRNA splicing profile, mRNA stability and translational efficiency, protein stability and degradation; and its protein's 3D configuration that may be regulated by acetylation, phosphorylation, glycosylation, and truncation. Epigenetic studies have elucidated fine tuning of gene expression by various factors including many phytonutrients and noncoding RNAs (85). For example, resveratrol induces SIRT1 which activates caspase 3 and 9 and induces apoptosis in fibroblast-like synovial cell line derived from

RA patients (86). Resveratrol-induced SIRT1 also modulated RANKL which modulated NF-kβ and inhibited osteoclastogenesis (87). Taken together, these data document multiple causes of RA or an RA flare and confounding factors that modulate its resolution. As aforementioned, the reported frequencies of these potential causes account for less than half of the induction of RA. Other mechanisms play an important role in RA onset.

The potential causes of RA flares need further elucidation, but we will assume that the aforementioned triggers of RA onset may also trigger the onset of a flare in susceptible RA patients. In addition, the postpartum period after pregnancy and the associated decline in endogenous immunomodulation due to pregnancy is associated with onset of a flare in 39% of women (88). Incidence of a flare was also significantly higher in patients with inadequate therapy adherence (89).

Testing of the Hypothesis

Complexity

Multiple causes help explain the complexity of the diagnosis and management of RA flares. As an initial step for developing a flowchart for identification of the cause of the recent RA diagnosis or immediate flare, we estimated the complexity of determining the cause at an initial visit. We assumed that the symptoms of each RA patient or RA flare may be triggered by one or more of the potential causes interacting with the patient's genetic risk factors, nutritional status, current immune response signature, epigenetic status, and detoxification ability. Although infection, physical trauma, and food sensitivities only account for approx. 46% of RA cases, we assumed that each of the 14 reported infectious agents (20, 21, 24), 20 potential food allergens (35, 37), physical trauma (18) and silica (43) can trigger RA in a small population: thus, at least 36 causes can elicit RA symptoms or induce an RA flare. We also assumed that any single or

combination of these 36 potential initiating events can cause RA or RA flares and that the order of events had no effect. Set theory indicated that the number of potential combinations of one or more n causes is 2^n – 1: one is subtracted because zero causes would not induce RA symptoms. For example, if RA can be initiated in patients by any combination of 3 causes, then the 7 combinations (A, B, C, AB, BC, CA, and ABC), or 2^3-1 combinations, represent the complexity of RA diagnosis. Similarly, 36 potential causes yield 2^{36}-1 possible combinations of one or more initiating events: 2^{36}-1 equals [68,719,476,736 – 1] or 68,719,476,735 possible combinations. The approximately 68 billion combinations of potential initiating events in any given RA patient would easily complicate the diagnosis, and overwhelm the challenges of elucidating the cause of an individual RA patient. Furthermore, these aforementioned events as well as other triggers (10) such as repeated exposure to smoke, air pollution, pesticides (47), organic volatile compounds, lack of exercise, emotional trauma, insufficient nutrition (e.g., low levels of vitamin D, omega 3 fatty acids, boron, selenium, zinc, vitamin C complex, vitamin E complex; and inadequate protein digestion), hormonal imbalance, and exposure to cold may exacerbate RA and lead to flares in various subsets of patients. Medications such as IL-12 and infliximab may also trigger a flare (90, 91). These latter triggers further expand the complexity of diagnosis and disease management.

Varied response

As aforementioned, the response to medications prescribed for RA varies and also depends on the criteria for improvement (4, 6-9, 77). A survey of current RA treatment regimens revealed that they were maintained in 80% of patients and their modification was linked to the lack of therapeutic response (6). For example, anti-TNF therapies provide improved disease management in many RA patients but an inadequate response occurs in 30-40% of RA patients (8). Anti-TNF agents have exacerbated RA disease (91), and reactivated tuberculosis and

infections with other mycoplasma species (58). Rituximab, which targets CD20-expressing B cells, improved disease symptoms in 82% using the EULAR criteria, but was associated with development of flare in 22% of patients within 6 months (9).

Nutritional supplements provide the necessary building blocks for healthy joints, but provide benefits only to those patients who have suboptimal levels of those nutrients (i.e. levels below their needs). Their benefit also depends on the patient's ability to absorb and assimilate them. For example, a sufficiently acid environment is needed in the stomach for efficient absorption of calcium and zinc; but some RA patients have hypochlorhydria (92) which may affect their nutritional status.

Direct testing of the hypothesis

This "RA cause affects response to therapy" or RACART hypothesis can be readily tested in retrospective, prospective, and case control studies. Presence of antibodies to the infectious agents can indicate exposure. A survey can request patients or their physicians to list and rank events that preceded RA symptoms and diagnosis by 0-6 months (18) or an RA flare by 0-7 days, For example, a recent survey indicated that many patients (490 / 1652) believed that their onset of RA was triggered by a specific event, including infection (16%), psychological trauma (4.4%), physical trauma (4.1%), surgery (2.8%), pregnancy (1.5%), and vaccination (1.2%) (93). In this patient population, the potential causes can be assessed for an association with responses to various therapies. Any potential associations can be adjusted for the patients' genetic risk factors, nutritional status, disease markers, detoxification ability, and lifestyle choices by multivariate regression analyses.

Implications of the RACART Hypothesis

Currently, the choice of medication to halt the progression of rheumatoid arthritis or calm a flare is a “trial and error” process (4). The response to a given drug regimen was significantly different depending on the measurement criteria. Regardless of the criteria, the percentage of complete responders was small (94). A questionnaire on recent events or exposures may help each patient elucidate the potential cause of RA or their recent RA flare. The indicated independent confounding factors may modulate the response of each class of therapies or each agent for a given cause. For example, RA patients with $GST^{null/null}$ phenotype would probably be less efficient in inactivating and eliminating environmental toxins than patients with $GST^{+/+}$ alleles. Boosting glutathione levels exogenously may augment the $GST^{null/null}$ patient’s ability to eliminate the perceived toxins (environmental, infection-induced, or allergy-associated). The role of these factors in promoting RA flares and the response to the therapies warrants further study. However, heart rate variability may act as a predictor of response (95). Interestingly, an increased pulse rate is a well-known symptom of the ingestion or exposure to an allergen. Different treatments may be more efficacious for specific triggers of the RA flare. Ebringer et al (96) suggests that RA patients with evidence of a *Proteus sp.* infection may benefit from concurrent anti-Proteus microbials, vegetarian diets, adequate water and cranberry juice. In an analogous manner, other autoimmune diseases such as Juvenile idiopathic inflammatory myopathies may also arise from multiple causes (97), and each potential cause may modulate the response to a therapeutic class and / or agent.

Implications

Daily treatment decisions in clinical practice still involves “trial and error” (4) due to unpredictable responses to therapy in a given patient. A flare is often managed by adding a

therapy that is new to that patient, a boost in the dosage of a current therapy and/or the addition of non-steroid anti-inflammatory drugs (5). Efficacy of medications range from 15%-82% but a medication may trigger flares in a low percent of patients (91). If the response to therapy is determined by the cause of the onset of RA or an RA flare, then the identification of the cause can refine the "trial and error" practice or "trial and learn" practice with a more narrow list of agents that will squelch the recently induced inflammatory and autoimmune response. Responses to a therapy chosen on the basis of the RACART hypothesis would be expected to be higher. Patient adherence to medication is not ideal (80) and would likely increase with improved medication choices due to higher efficacy. The side effect profile would be expected to decline. Improved responses and greater patient adherence would lead to higher remission rates and improved quality of life (80, 98). The cost-effectiveness of treatment would be higher than choosing the treatment based on the current "trial and error" pyramid. Thus, elucidation of the relationship between cause of rheumatoid arthritis and response to a given therapy may improve remission rates, quality of life, and cost effectiveness of therapy.

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Conflict of interests

Drs. K.L. Molnar-Kimber and C.T. Kimber have no conflicts of interest.

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Table 1. The potential role of the RA cause on the type of joint tissue damage, innate immune system, adaptive immune response, and molecular mimicry

Probable cause	Effect on Joint Tissue	Innate immune response	Adaptive Immune System	Molecular mimicry (MM)
Physical trauma	Damage tissue, expose new antigens (23).	Inflammatory, wound healing response	Less involved in normal healing of bone fractures.	low
Infection	Infectious agent damages tissues, and possibly joints. Exposes new antigens such as citrullinated proteins (23).	Inflammatory cytokines involved in response to infection	Type of response depends on type of pathogen and location of infection. PTPN22 variant shortens duration of TCR response (14).	Migrating T cells specific for an infectious agent can find similar antigens in joints (21, 23). Possible MM (21, 23).
Allergy	Unknown mechanism for affecting joint tissues.	Offending food increases TNF alpha and IL-1 in RA (33). Mast cells release IL-17A in RA (40).	Correlation not investigated in 5% of patients with dietary sensitivities (33).	Possible in subset of patients, but MM did not always occur (35, 37)
Environmental toxin*	Unknown mechanism for transporting toxins to joints.	Modulates innate immunity	May modulate normal immune response (10).	Possible MM (10, 23).

* Environmental toxins such as smoking, pesticides, air pollution, organic volatile compounds.