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Effects of Smoking on Immunologic and Skeletal Mechanisms Involved in Rheumatoid Arthritis and Responses of Various Biologic Therapies for RA

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Abstract

Smoking is considered a major risk factor in the onset of rheumatoid arthritis. Smokers who also carry the HLA-DR4 shared epitope have a higher risk of development of RA. Smoking releases more than 4000 compounds which not only affect the cardiovascular and respiratory systems but also bone and joint health. Smokers have a higher risk for bone fractures, development of osteoporosis, and degeneration of intervertebral discs. Bone fractures of most smokers heal slower than those of most controls. Smoking also lowers bone mineral density, increases production of proinflammatory cytokines, and augments the risk of citrullination of proteins in the lungs, and possibly in the joints. RA patients who generated antibodies to cyclic citrullinated proteins (CCP) have a higher risk for joint erosions. Although response rates are significantly higher in nonsmoking early RA patients than nonsmoking RA patients with long-standing disease, response rates are not significantly improved in smoking early RA patients. Smoking has decreased response rates to TNF blockers. Additional studies indicated that smoking significantly reduced the response rate of infliximab but not etanercept or adalimumab in RA patients. Because one TNF blocker (infliximab) had significantly lower response rates in a subpopulation of RA patients (smokers versus never smokers) than two distinct TNF blockers, criteria for the development and approval of biosimilars may need to include in vivo trials as well as a demonstration of activity against the primary target (e.g. TNFα). Although the most straight forward recommendation is for patients to stop smoking, investigations on the effect of smoking on response to therapies may serve as a model for elucidating the effect of other environmental contaminants such as air pollution on the response to treatment of flares in RA patients.

Keywords: Smoking; Rheumatoid arthritis; TNFα blockers; Infliximab; Etanercept; Adalimumab; Biosimilars

Introduction

Prognosis for many rheumatoid arthritis (RA) patients has vastly improved in the last two decades due to the introduction of targeted biologic therapies and the improved understanding of the role of lifestyle choices. Long term remission of RA is now a prominent goal for RA management. The ultimate goal is to modulate a critical pathway that subsequently resolves the autoimmune response without globally crippling the immune response of the RA patient to pathogenic agents and transformed cells.

Onset of rheumatoid arthritis is a multistep process [1]. Predisposing factors such as genetic susceptibilities, environmental factors, and immune modulators increase the risk of development of RA [1,2] (Figure 1). Alleles of several genes that modulate the response to external and self antigens (e.g. HLA-DR4 shared epitope, $GST1^{null}$) increase the risk of RA onset. Low concentrations of vitamin D and essential omega 3 fatty acids may skew an immune response to a microbial threat, and delay resolution of the inflammatory response [3-7]. These predisposing factors can alter gene expression by epigenetic and posttranslational processes [1,8-10]. Multiple causes can initiate the onset of RA in susceptible individuals who are under proinflammatory conditions [2,8]. Previously reported triggering events include infection [11,12], bone fracture [13], exacerbation of food sensitivities [14,15], and overexposure to smoking [16] or other environmental toxins. These events often occur concurrently with a significant emotional event. RA progression is associated with greater alterations in cytokine profiles and regulatory T cells compared to those of healthy controls and patients at RA onset [17].

Because the cause of RA onset or flares in any given patient is unknown to the physician, immunotherapies have traditionally targeted molecules that reduce an aberrant immune response. Current immunotherapies include the TNF blockers (etanercept, infliximab, adalimumab, certolizumabpegol, golimumab), the IL-1 receptor antagonist (anakinra), a blocker of costimulation (abatacept), an IL-6R blocker, and a monoclonal antibody (mAb) that depletes $CD20^{+}$ B cells (rituximab). Efficacy of the biologics ranges from 15%-82% of patients. Because some patients on biologic therapy do not improve and a few patients experience a flare or worse symptoms [18], pursuit of biological markers that correlate with the response to therapy are ongoing. No markers have provided sufficient correlation to warrant their incorporation into clinical decisions. The choice of therapy remains a "trial and error" or trial and learn scenario [19]. Elucidation of a treatment with the highest frequency of efficacy for a given RA subpopulation would improve the current "trial and error" decisions for that subgroup. RA patients who currently smoke comprise approx. 20-27% of the British and Swedish RA populations, respectively. Smokers in the US comprised 20.8% of the adult population in 2008, similar to the prevalence of smokers (20.9%) in 2004 [20]. This review summarizes the effect of smoke on the overall RA disease, the immunologic and skeletal mechanisms involved in RA, and the efficacy of various immunotherapies in the subpopulation of RA patients who

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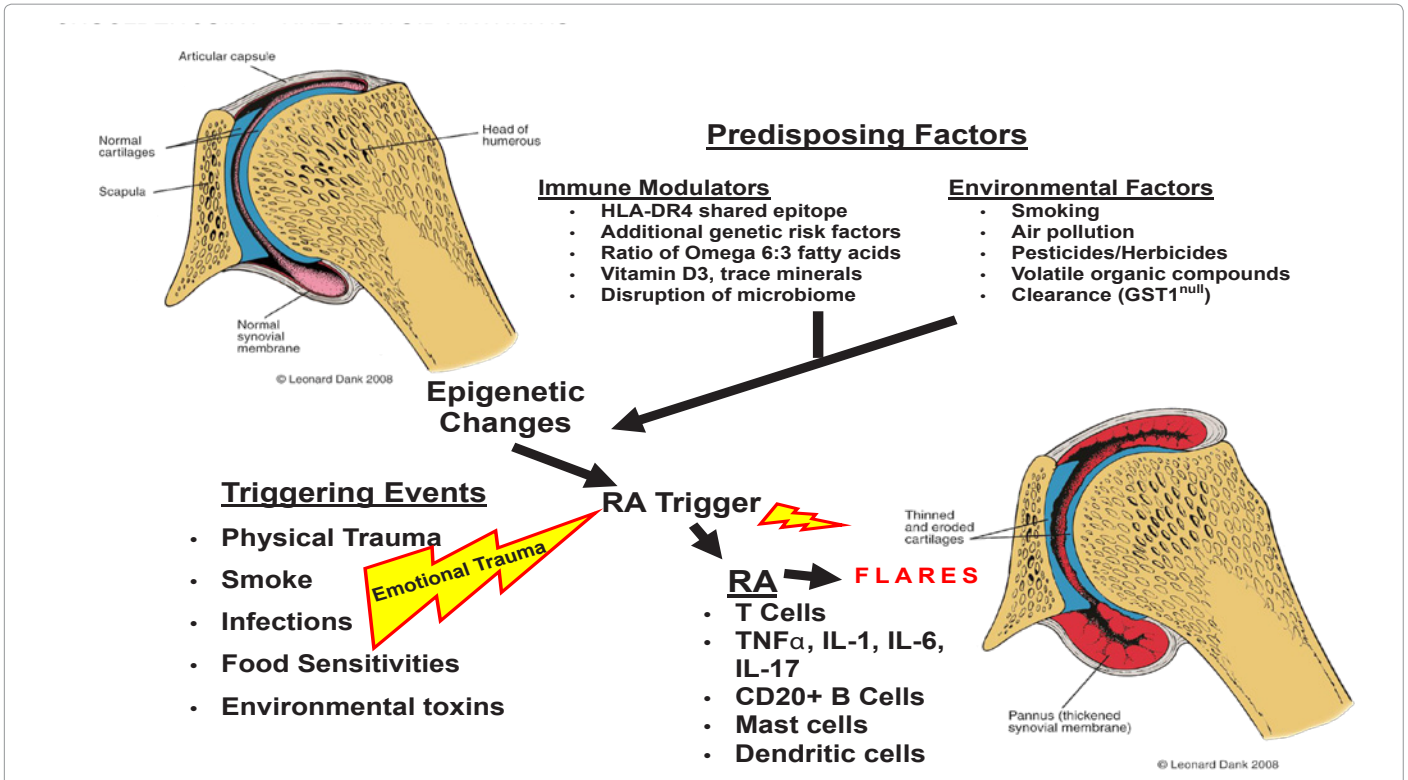

Figure 1: Development of the rheumatoid arthritis and the onset of flares involves a multistep process. Predisposing factors were categorized into immune modulators and environmental factors. Genetic risk factors include genes in immune modulation (e.g. HLA-DR4 shared epitope, PTPN22, TNFα polymorphisms and the detoxification pathways (e.g. GST1^{null} [52]) [1] and references therein). Diets that contain > 5:1 omega 6 to omega 3 fatty acids increase the risk for prolonged inflammation [6]. One of these potential triggering events often coupled with an emotional stress is associated with the onset of RA, although other causes which induce 34-54% of RA cases have yet to be elucidated [8]. Patients exposed to additional triggering events can experience further RA progression and flares. This figure was inspired by Figure 1 from McInnes and Schett [1].

are smokers. This review also notes gaps in the knowledge of the effects of immunotherapies on smokers.

Smoking's Effect on RA Disease

Smoking is a major risk factor for RA onset worldwide and is estimated to be a major factor of RA onset in about 1 in 5 RA patients in Sweden [21] and up to 35% of RA patients who exhibit anti-citrullinated protein antibodies [16,21]. Longer duration and higher intensity of smoking increased the risk of onset of RA [22], especially ACPA positive RA [23]. Smoking was associated with earlier age of onset of RA [24,25]. Smoking also hastened RA progression [26], especially radiographic progression in some studies [27,28] but not others [25,29].

In early RA patients, smoking was associated with higher RA disease activity (number of tender joints, Larsen's score, DAS-28, higher frequency of autoantibodies), and severity independent of age, alcohol consumption, follow-up duration, and gender [23,24,30]. Prospective monitoring of 100 early RA patients for 2 years indicated that RA disease activity (swollen and tender joints, pain) increased stepwise from never smokers to former smokers to current smokers [31]. Heavy smoking (≥20 packs/yr) was significantly associated with greater loss of daily functioning (higher HAQ score, lower grip strength) and development of rheumatoid nodules [28].

Smoking was positively correlated with Rheumatoid Factor (RF) levels, especially IgA RF in one study [28], but not another study [31]. Former or current smokers developed IgA RF more often than nonsmokers [31]. IgARF is associated with higher radiological score for joint erosion [31].

Smoke

Cigarette smoke (CS) contains a mixture of approximately 4000 toxic substances including nicotine, polycyclic aromatic hydrocarbons (carcinogens), unsaturated aldehydes, solvents, free radicals, carbon monoxide, and other gases [32]. Nicotine concentration in plasma is <1 mcg/mL in light to heavy smokers while tissues harbor 1-10 mcg/g [33]. Cigarette smoke induces reactive nitrogen species, reactive oxygen species, and reactive sulfur species which can damage proteins, lead to exposure of novel epitopes, and induce antibodies against self-proteins such as type II collagen [34]. In addition, cigarette smoke increases the probability of citrullination of mucosal proteins by peptidyl arginine deiminase type IV (PADI4). PADI4 is overexpressed in synovial fluid of RA patients compared to samples of osteoarthritis [35]. Novel epitopes in the citrullinated proteins (citrullinated fibrinogen, alpha-enolase, vimentin, type II collagen, and fillaggrin) can stimulate significant titers of anti-citrullinated protein antibodies (ACPA). High titers of ACPAs in RA patients correlate with a higher incidence of erosions [36].

Smoking and Genetic Susceptibility to RA

In monozygotic twin studies, concordance rate of RA ranges from 12% to 30% [37,38]. Since most twins are raised by their family in the same house with similar diets, lifestyle choices, and environmental exposures, the concordance rate not only includes the contribution of genetic susceptibilities but also subtle differences in the interactions

between their genetics and their predisposing factors, emotional influences [39], smoking [40], and the initiating triggers of RA.

Genetic susceptibility to RA can be grouped into (i) genes that influence the immune and inflammatory responses, (ii) genes that encode enzymes for generation of novel self-antigens [41], and (iii) genes in the detoxification system. Smoking has been shown to increase the risk for developing RA, especially in people who contain the HLA-DRB1 shared epitope in most ethnic groups including Koreans [42], Danes [43], but not all populations such as Brazilians [44]. The shared epitope is found in 31%-70% of RA patients of most ethnic groups, but present in greater than 90% in Native American RA patients [45] and references therein. The shared epitope (SE) is located in the third hypervariable region of HLA-DRB1 (amino acids 70-74) in the following alleles: DRB1*0401, DRB1*0404, DRB1*0405, DRB1*0408, DRB1*0101, DRB1*102, DRB1*1001 and DRB1*1402. Patients who are SE homozygotes and heavy smokers had a 7.47 fold [46] to 50 fold higher risk of developing RA than nonsmoking, SE negative patients [43,47]. Southern European smokers had an earlier onset of RA [24]. Some populations of heavy smokers exhibited a higher risk for anti-citrullinated protein antibody positive RA [47] or for RF positivity and rheumatoid nodules [48] but not ACPA-negative RA. Smokers had a poorer response rate to medication than previous or never smokers in some studies [49] but not all studies [29]. One potential mechanism is that some smokers may induce citrullinated proteins in the joints since smokers induce citrullinated proteins in bronchoaveolar lavage where as nonsmokers did not [47].

ACPA seropositivity is associated with a higher incidence of erosions in RA patients but is not dose dependent [50]. Smokers with RA had significantly higher titers of ACPA than nonsmokers [50]. Analysis of polymorphisms at the PADI4 show that a haplotype containing three polymorphisms in *PPDI4* genepadi4_89 (rs11203366), padi4_90 (rs11203367), and padi4_92 (rs874881) in Koreans is significantly associated with risk of RA development in both anti-CCP positive RA and anti-CCP negative RA patients [42]. No association with single PAD4 polymorphisms in Caucasians has been reported. Surprisingly, risk of RA in individuals with the PADI4 haplotype or single alleles were not associated with smoking [51].

Glutathione S transferases (GST) and hemeoxygenase 1 (HMOX1) genes encode enzymes involved in inactivation of toxins and their subsequent removal. GST conjugates glutathione to cytotoxic carcinogens and metabolites for efficient excretion. GSTM1 null allele is associated with higher risk for RA [52]. Since smoking produces many toxic substances, Bohanec et al. proposed that the null allele of GSTM1 may increase the risk of RA in smokers [53]. The presence of the GSTM1 null allele increased the risk of RA onset in SE homozygotes approx. 8 fold [53]. Smoking increased the probability of Rheumatoid Factor (RF) production in patients with the null allele of GSTM1 [54]. Inducible HMOX1 enzyme, which catabolizes heme into unbound iron, carbon monoxide, and biliverdin, is overexpressed in lesions in synovial tissues from RA patients compared to those of other subjects [55]. It exhibits anti-oxidant, anti-inflammatory and cytoprotective activities. Nicotine reduces HMOX1 levels while increasing proinflammatory cytokines [55]. One polymorphism in the HMOX1 gene promoter (rs2071746) reduces its expression [56].

Smoking and Joints

Smoking has a broad range of negative effects on bone metabolism, including profound bone loss [57]. Smokers have a higher risk for bone fractures [58], development of osteoporosis [57,59], degeneration of intervertebral discs [58,60], and slower healing of bone fractures [58,61]. Bone mineral density values were significantly lower in smokers than those in nonsmokers [62]. Proposed mechanisms include vasoconstriction by nicotine, reduced exchange of nutrients and waste products [60], and direct effects on cells in the joints. Water soluble smoke concentrate (WSSE) reduces cell viability and metabolism of human disc cells, induces an inflammatory response, augments expression of metalloproteinases, and decreases active matrix synthesis and expression of its structural genes in human disc cells [60]. Smokers often have normal levels of markers for bone formation but augmented markers for bone remodeling [57] which is consistent with observations of periodontal bone loss in smokers [62]. Nicotine stimulated metalloproteinase 9 (MMP-9) from a human neutrophil differentiation model, consistent with higher MMP-9 levels found in smokers [63]. It also reduced the size of the oxidative burst from neutrophils and inhibited bacterial killing [63]. Nicotine significantly stimulated TNFα secretion from human osteoblasts [64].

Total protein content, insulin-like growth factor 1 (IGF-1), and beta fibroblast growth factor (bFGF) were significantly reduced in synovial tissue of smokers compared to those of nonsmokers [65]. Smoking significantly reduces the early secretion of tumor growth factor (TGFβ) [61] and TNFα levels [66].

Smoking and Immune Responses

Cigarette smoke increases the risk of pulmonary infections, lung cancer, bacterial and fungal infections, as well as the onset of RA. Cigarette smoke modulates both the innate and acquired immune responses. Its effect on cytokines and cell types can differ depending on the species, dose, and conditions of the assay (in vivo, ex vivo, nutritional status, in vitro, smoke components, stimuli and genetic susceptibility). Human lymphocytes exposed to mild (30 mmHg) but not high (200 mmHg) concentrations of smoke showed NF-κB activation, reduction of intracellular glutathione levels, and subsequent enhanced inflammatory gene expression [67,68]. The effects of smoke exposure tracked the nitric oxide (NO) dose-dependent response: low doses activated NF-κB while high NO levels inhibited its activation [68]. Bronchoalveolar lavage (BAL) derived macrophages of smokers showed less clearance of apoptotic cells, reduced glutathione levels, inefficient antigen presentation, and increased proinflammatory cytokines compared to those of healthy controls [69]. In contrast, macrophages from nonsymptomatic smokers showed significantly lower mRNA levels of IL-6, TNFβ, interferon gamma, IL-13, and various chemokines (CCL5, CCL3, CCL4, and CCL20) [70]. LPS-stimulated BAL-derived alveolar macrophages from smokers showed reduced secretion of TNFα, IL-6, and IL-8 [71]. However, smoking augments the production of proinflammatory TNFα in the serum [72], but reduces the TNFα production from plasmacytoid dendritic cells *in vitro* [73].

In addition, smoking significantly affects the transcription of 324 genes in human lymphocytes, including 66 genes involved in cell cytotoxicity (47 negatively correlated and 19 positively correlated), 38 involved in the immune response (30 negatively associated and 8 positively associated), 18 genes for an inflammatory response, 11 in NK cell signaling, 31 for cell activation, 29 for cell adhesion, and 27 for lymphocyte cell proliferation among others [74]. Thus, modulation of additional genes may contribute to smoking's effect on RA onset and progression.

Smoking may also affect the gut associated lymphoid tissue (GALT) as smokers develop Crohn's disease at a 1.75 fold higher rate than nonsmokers [75,76]. Interestingly, smoking reduces the rate of ulcerative colitis [75,76]. Since NSAIDs also induce inflammation of the gut and increase intestinal permeability, RA patients who are smokers and utilize NSAIDs for pain relief may be at a higher risk for development of food sensitivities or allergies which can exacerbate RA symptoms in some patients [14].

Smoking and Immunotherapies

Immunotherapies can be grouped into 2 categories: general targeted therapies and antigen-specific immunotherapies. The effect of smoking on responses to therapy in RA has not been systematically examined for most immunotherapies. Although treatment of nonsmokers who were recently diagnosed with RA significantly improved their Disease Activity score in an inverse relationship to duration of RA, smoking obscures or eliminates this effect [49]. Thus, a window of opportunity to obtain higher therapeutic responses in very early RA patients was not evident in smokers [49].

Smoking and General Targeted Immunotherapies

General targeted immunotherapies include inhibitors of cytokines (TNF blockers, IL-1Ra, IL-6 blocker, IL-17 blocker), disruptors of costimulatory signals for T cell activation (Abatacept), a monoclonal antibody (mAb) specific for CD20 that depletes $CD20^+$ B cells (Rituximab), and stimulators of regulatory T cells. Overall response rates to biologics for patients resistant to methotrexate is approximately 60-70% and no markers currently predict response to a given biologic although several sets of gene expression profiles are under investigation [77].

Smoking did not significantly increase the rate of switching from a biologic treatment [78]. The most common reasons for switching from a biologic treatment (47%) were inefficacy (43%) and adverse reactions (48%) which included malignancy, rash, infections, or cardiovascular complications) [78].

TNF Blockers

The advent of TNF blockers has revolutionized the treatment of RA. Five currently marketed TNF blockers (etanercept, infliximab, adalimumab, and recently golimumab, certolizumabpegol) reduce TNF signaling by binding TNFα and blocking the binding of TNFα to its cell-bound receptors. TNF blockers utilize three basic mechanisms to remove TNFα from fluids: etanercept is a fusion protein consisting of a soluble TNF receptor 2 linked to a Fc component of human immunoglobulin; infliximab is a mouse-human chimeric monoclonal antibody (mAb) and adalimumab and golimumab are humanm Ab that react with TNFα; certolizumabpegol is a pegylated Fab fragment of a humanized mAb that binds TNFα. Etanercept, infliximab, adalimumab, golimumab provide a moderate or good EULAR response in approximately 50-75% of RA patients in the initial 6 months [79-81]. Certolizumabpegol appears to have a similar efficacy and a higher burden of adverse events [82].

Current smokers with early RA were less likely to respond to treatment with TNF blockers [79,83-85]. Saevarsdottir et al. [84] examined the effect of smoking on response to therapy in the pool of early RA patients who had received TNF blocker therapy (infliximab (n=199); etanercept (n=136); adalimumab (n=66)). Current smokers had a significantly lower rate of good response to TNF blockers after 3 months (29%) than never smokers (43%, P=0.05). Previous smokers had an intermediate rate (39%) which was similar to never smokers. Current smoking remained a predictor of higher risk for poor response in multivariate regression analysis at both 3 months (OR: 0.52; CI: 0.29-0.96) and at 6 months (OR: 0.55, CI: 0.31-0.96) in this study population. Because the responses of the patients on TNF blockers were pooled, the efficacy of the three TNF blocking agents in smokers was not compared [84]. The effect of smoking on the response rates of golimumab and certolizumabpegol in RA patients who are smokers remains unclear.

Hyrich et al. examined the factors that correlated with response of RA patients to infliximab (n=1612) or to etanercept (1267) at 6 months [79]. Higher baseline HAQ score, but not age, gender, disease duration, or rheumatoid factor status, was associated with a poorer response to either etanercept or infliximab. In contrast, concurrent use of NSAIDS was associated with a higher EULAR response to these two TNF blockers. In addition, current smokers with RA who were treated with infliximab but not etanercept, were less likely to respond adequately [79]. Multivariate regression analysis indicated that current smoking in infliximab-treated RA patients was a significant inverse predictor of EULAR responses (OR: 0.77, CI: 0.60-0.99); but smoking in etanercept-treated RA patients did not significantly affect responses (OR:1.00, CI 0.77-1.31) [79].

Soderlin et al. [85] compared the 3 month, 6 month, and 12 month efficacy of the three TNF blockers in RA patients who were previous (n=345) or current smokers(n=216) to those who never smoked (n=373). Previous and current smokers had a worse response to TNF blockers as measured by the Simplified Disease Activity Index (SDAI) at 3 months, 6 months, and 12 months than RA patients who were never smokers according to univariate analysis [85]. Whereas the SDAI response to adalimumab was equivalent to the response to etanercept at 3 months, 6 months, and 12 months in this RA patient population according to multivariate analysis, the SDAI response to infliximab was significantly reduced at 3 months (OR=0.56, CI 0.35-0.90), 6 months (OR=0.29, CI 0.15-0.53) and at 12 months (OR=0.36, CI 0.18-0.75) [85]. Heavy smokers showed the least benefit as a group [85].

Two studies [79,85] indicated that the efficacy of infliximab is less in smokers than nonsmokers. Potential mechanisms for the reduced therapeutic benefit of infliximab in smokers include increased citrullination of proteins in smokers, the potential of the citrullinated proteins to induce crossreactive autoantibodies to joint constituents (ACPA), the higher burden of toxins, and higher nutritional needs (e.g. ascorbate, folate) [86-88]. The mechanisms that induce the differential response rate of etanercept and adalimumab in RA patients that are smokers compared to that of infliximab are unclear. The three TNF blockers appear to primarily target soluble TNFα rather than cell associated TNFα. Differences in binding affinities between the three TNF inhibitors do not appear to account for differential response rates in smokers: the binding affinity of etanercept (Kd=0.4 pM) to TNFα was 10-20 fold greater than the affinity of infliximab (4.2 pM) or adalimumab (8.6 pM), yet adalimumab shows similar efficacy in RA patients who are smokers as etanercept [85]. Another possible mechanism is the effect of smoking on apparent clearance of the TNF blockers [89] which can be addressed in future studies.

The effect of smoking on response rate of patients who are APCA-positive or ACPA-negative and treated with TNF blockers has not been reported. Because one TNF blocker (infliximab) had significantly lower response rates in a subpopulation of RA patients (smokers versus never smokers) than two distinct TNF blockers, criteria for the development and approval of biosimilars may need to include in vivo trials as well as

a demonstration of activity against the primary target (e.g. TNF).

Effect of Smoking on Response to IL-1Receptor Antagonist (IL-1Ra), IL-6 Blocker, Anti CD-20 Biologic Therapy, and Emerging Therapies

The effect of smoking on the response to treatment of RA patients with IL-1Receptor Antagonist (IL-1Ra) [90], IL-6 blocker [91], anti CD-20 biologic therapy [92-94], or emerging therapies (JAK inhibitors, cell therapy, tolerogenic dendritic cells, dnaJP1, tolerogenic collagen type II) has not been studied. However, smoke can affect IL-1Ra plasma concentrations [95], IL-1 and IL-1Ra serum concentrations [96-98], IL-6 production [99], and the probability of developing ACPA antibodies (which are a predictor for efficacy with anti-CD20 biologic therapy) [92-94]. In addition, smoking induces heme oxygenase-1 (HO-1) via a JAK2 dependent cascade [100] (which are modulated by kinase inhibitors), does not significantly affect the harvest size of primitive progenitor cells from healthy individuals [101], reduces efficacy of hematopoetic stem cell therapy for cancer [102], and lowers the efficiency of antigen presentation [69]. Thus, studies that directly compare the efficacy of any biologic therapy or emerging therapies in RA patients who are smokers versus the efficacy in nonsmoking RA patients are needed to assist clinicians in choosing medications with the highest probability of efficacy for RA patients who are smokers.

Conclusions

Exposure to smoke is a major factor in the onset of rheumatoid arthritis in about 20% of Swedish patients, especially those who carry the HLA-DR4 shared epitope. Smoking releases more than 4000 compounds, some of which affect bone and joint health. Smokers have a higher risk for bone fractures, development of osteoporosis, degeneration of intervertebral discs, and slow healing of bone fractures. Smoking lowers bone mineral density, increases secretion of proinflammatory cytokines, and augments the risk of citrullination of proteins,which increases the risk for joint erosions. Response rates for smokers are similar between early RA patients and those with chronic RA history. Smokers have lower response rates to the TNFα blocker, infliximab but not etanercept or adalimumab than nonsmokers. Criteria for biosimilars may need to include studies that assess responses in smokers as well as demonstrate binding activity to a target protein. The effect of smoking on the response rates to other current immunotherapies or to emerging therapies is currently unknown. Although the most straight forward recommendation is for patients to stop smoking, investigations on the effect of smoking on therapeutic response rates may serve as a model for elucidating the effect of other environmental contaminants such as air pollution, formaldehyde, and volatile organic compounds on the response to treatment of environmental toxin-induced flares in RA patients.

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References

1. McInnes IB, Schett G (2011) The pathogenesis of rheumatoid arthritis. N Engl J Med 365: 2205-2219.
2. Deane KD, Norris JM, Holers VM (2010) Preclinical rheumatoid arthritis: identification, evaluation, and future directions for investigation. Rheum Dis Clin North Am 36: 213-241.
3. Laragione T, Shah A, Gulko PS (2012) The vitamin D receptor regulates rheumatoid arthritis synovial fibroblast invasion and morphology. Mol Med 18: 194-200.
4. Knekt P, Heliövaara M, Aho K, Alfthan G, Marniemi J, et al. (2000) Serum selenium, serum alpha-tocopherol, and the risk of rheumatoid arthritis. Epidemiology 11: 402-405.
5. Pedersen M, Stripp C, Klarlund M, Olsen SF, Tjønneland AM, et al. (2005) Diet and risk of rheumatoid arthritis in a prospective cohort. J Rheumatol 32: 1249-1252.
6. Simopoulos AP (2008) The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Exp Biol Med (Maywood) 233: 674-688.
7. Serhan CN (2009) Systems approach to inflammation resolution: identification of novel anti-inflammatory and pro-resolving mediators. J Thromb Haemost 7 Suppl 1: 44-48.
8. Molnar-Kimber KL, Kimber CT (2012) Each type of cause that initiates rheumatoid arthritis or RA flares differentially affects the response to therapy. Med Hypotheses 78: 123-129.
9. Javierre BM, Hernando H, Ballestar E (2011) Environmental triggers and epigenetic deregulation in autoimmune disease. Discov Med 12: 535-545.
10. Strietholt S, Maurer B, Peters MA, Pap T, Gay S (2008) Epigenetic modifications in rheumatoid arthritis. Arthritis Res Ther 10: 219.
11. Ebringer A, Rashid T, Wilson C (2010) Rheumatoid arthritis, Proteus, anti-CCP antibodies and Karl Popper. Autoimmun Rev 9: 216-223.
12. Leirisalo-Repo M (2005) Early arthritis and infection. Curr Opin Rheumatol 17: 433-439.
13. Al-Allaf AW, Sanders PA, Ogston SA, Marks JS (2001) A case-control study examining the role of physical trauma in the onset of rheumatoid arthritis. Rheumatology (Oxford) 40: 262-266.
14. Darlington LG, Ramsey NW (1991) Diets for rheumatoid arthritis. Lancet 338: 1209-1210.
15. Panush RS (1990) Food induced ("allergic") arthritis: clinical and serologic studies. J Rheumatol 17: 291-294.
16. Källberg H, Ding B, Padyukov L, Bengtsson C, Rönnelid J, et al. (2011) Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis 70: 508-511.
17. de Paz B, Alperi-López M, Ballina-García FJ, Prado C, Gutiérrez C, et al. (2010) Cytokines and regulatory T cells in rheumatoid arthritis and their relationship with response to corticosteroids. J Rheumatol 37: 2502-2510.
18. Rozenbaum M, Boulman N, Slobodin G, Ayubkhanov E, Rosner I (2006) Polyarthritis flare complicating rheumatoid arthritis infliximab therapy: a paradoxic adverse reaction. J Clin Rheumatol 12: 269-271.
19. Scherer HU, Dörner T, Burmester GR (2010) Patient-tailored therapy in rheumatoid arthritis: an editorial review. Curr Opin Rheumatol 22: 237-245.
20. Center for Disease Control and Prevention (2012) U.S. Adult Smoking. In: Services UDoHaH, editor.
21. Klareskog L, Gregersen PK, Huizinga TW (2010) Prevention of autoimmune rheumatic disease: state of the art and future perspectives. Ann Rheum Dis 69: 2062-2066.
22. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, et al. (2010) Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 69: 70-81.
23. Yahya A, Bengtsson C, Lai TC, Larsson PT, Mustafa AN, et al. (2011) Smoking is associated with an increased risk of developing ACPA-positive but not ACPA-negative rheumatoid arthritis in Asian populations: evidence from the Malaysian MyEIRA case-control study. Mod Rheumatol.
24. Papadopoulos NG, Alamanos Y, Voulgari PV, Epagelis EK, Tsifetaki N, et al. (2005) Does cigarette smoking influence disease expression, activity and severity in early rheumatoid arthritis patients? Clin Exp Rheumatol 23: 861-866.
25. Finckh A, Dehler S, Costenbader KH, Gabay C; Swiss Clinical Quality

Management project for RA (2007) Cigarette smoking and radiographic progression in rheumatoid arthritis. Ann Rheum Dis 66: 1066-1071.

26. Criswell LA, Merlino LA, Cerhan JR, Mikuls TR, Mudano AS, et al. (2002) Cigarette smoking and the risk of rheumatoid arthritis among postmenopausal women: results from the Iowa Women's Health Study. Am J Med 112: 465-471.

27. Ruiz-Esquide V, Gómez-Puerta JA, Cañete JD, Graell E, Vazquez I, et al. (2011) Effects of smoking on disease activity and radiographic progression in early rheumatoid arthritis. J Rheumatol 38: 2536-2539.

28. Masdottir B, Jónsson T, Manfredsdottir V, Víkingsson A, Brekkan A, et al. (2000) Smoking, rheumatoid factor isotypes and severity of rheumatoid arthritis. Rheumatology (Oxford) 39: 1202-1205.

29. Westhoff G, Rau R, Zink A (2008) Rheumatoid arthritis patients who smoke have a higher need for DMARDs and feel worse, but they do not have more joint damage than non-smokers of the same serological group. Rheumatology (Oxford) 47: 849-854.

30. Söderlin MK, Petersson IF, Bergman S, Svensson B; BARFOT study group (2011) Smoking at onset of rheumatoid arthritis (RA) and its effect on disease activity and functional status: experiences from BARFOT, a long-term observational study on early RA. Scand J Rheumatol 40: 249-255.

31. Manfredsdottir VF, Vikingsdottir T, Jonsson T, Geirsson AJ, Kjartansson O, et al. (2006) The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis. Rheumatology (Oxford) 45: 734-740.

32. Baka Z, Buzás E, Nagy G (2009) Rheumatoid arthritis and smoking: putting the pieces together. Arthritis Res Ther 11: 238.

33. Hallquist N, Hakki A, Wecker L, Friedman H, Pross S (2000) Differential effects of nicotine and aging on splenocyte proliferation and the production of Th1- versus Th2-type cytokines. Proc Soc Exp Biol Med 224: 141-146.

34. Winyard PG, Ryan B, Eggleton P, Nissim A, Taylor E, et al. (2011) Measurement and meaning of markers of reactive species of oxygen, nitrogen and sulfur in healthy human subjects and patients with inflammatory joint disease. Biochem Soc Trans 39: 1226-1232.

35. Chang X, Zhao Y, Sun S, Zhang Y, Zhu Y (2009) The expression of PADI4 in synovium of rheumatoid arthritis. Rheumatol Int 29: 1411-1416.

36. Mathsson L, Mullazehi M, Wick MC, Sjöberg O, van Vollenhoven R, et al. (2008) Antibodies against citrullinated vimentin in rheumatoid arthritis: higher sensitivity and extended prognostic value concerning future radiographic progression as compared with antibodies against cyclic citrullinated peptides. Arthritis Rheum 58: 36-45.

37. Järvinen P, Aho K (1994) Twin studies in rheumatic diseases. Semin Arthritis Rheum 24: 19-28.

38. Aho K, Koskenvuo M, Tuominen J, Kaprio J (1986) Occurrence of rheumatoid arthritis in a nationwide series of twins. J Rheumatol 13: 899-902.

39. Boscarino JA, Forsberg CW, Goldberg J (2010) A twin study of the association between PTSD symptoms and rheumatoid arthritis. Psychosom Med 72: 481-486.

40. Silman AJ, Newman J, MacGregor AJ (1996) Cigarette smoking increases the risk of rheumatoid arthritis. Results from a nationwide study of disease-discordant twins. Arthritis Rheum 39: 732-735.

41. Kochi Y, Thabet MM, Suzuki A, Okada Y, Daha NA, et al. (2011) PADI4 polymorphism predisposes male smokers to rheumatoid arthritis. Ann Rheum Dis 70: 512-515.

42. Bang SY, Lee KH, Cho SK, Lee HS, Lee KW, et al. (2010) Smoking increases rheumatoid arthritis susceptibility in individuals carrying the HLA-DRB1 shared epitope, regardless of rheumatoid factor or anti-cyclic citrullinated peptide antibody status. Arthritis Rheum 62: 369-377.

43. Pedersen M, Jacobsen S, Garred P, Madsen HO, Klarlund M, et al. (2007) Strong combined gene-environment effects in anti-cyclic citrullinated peptide-positive rheumatoid arthritis: a nationwide case-control study in Denmark. Arthritis Rheum 56: 1446-1453.

44. Yazbek MA, Barros-Mazon Sd, Rossi CL, Londe AC, Costallat LT, et al. (2011) Association analysis of anti-Epstein-Barr nuclear antigen-1 antibodies, anti-cyclic citrullinated peptide antibodies, the shared epitope and smoking status in Brazilian patients with rheumatoid arthritis. Clinics (Sao Paulo) 66: 1401-1406.

45. Nepom B, King RA (2002) Rheumatoid Arthritis. In: King RA, Rotter JI, Motulsky AG (eds) The Genetic Basis of Common Diseases. (2ndedn) Oxford University Press, New York.

46. Karlson EW, Chang SC, Cui J, Chibnik LB, Fraser PA, et al. (2010) Gene-environment interaction between HLA-DRB1 shared epitope and heavy cigarette smoking in predicting incident rheumatoid arthritis. Ann Rheum Dis 69: 54-60.

47. Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, et al. (2006) A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 54: 38-46.

48. Naranjo A, Toloza S, Guimaraes da Silveira I, Lazovskis J, Hetland ML, et al. (2010) Smokers and non smokers with rheumatoid arthritis have similar clinical status: data from the multinational QUEST-RA database. Clin Exp Rheumatol 28: 820-827.

49. Söderlin MK, Bergman S; BARFOT Study Group (2011) Absent "Window of Opportunity" in smokers with short disease duration. Data from BARFOT, a multicenter study of early rheumatoid arthritis. J Rheumatol 38: 2160-2168.

50. Lee DM, Phillips R, Hagan EM, Chibnik LB, Costenbader KH, et al. (2009) Quantifying anti-cyclic citrullinated peptide titres: clinical utility and association with tobacco exposure in patients with rheumatoid arthritis. Ann Rheum Dis 68: 201-208.

51. Bang SY, Han TU, Choi CB, Sung YK, Bae SC, et al. (2010) Peptidyl arginine deiminase type IV (PADI4) haplotypes interact with shared epitope regardless of anti-cyclic citrullinated peptide antibody or erosive joint status in rheumatoid arthritis: a case control study. Arthritis Res Ther 12: R115.

52. Yun BR, El-Sohemy A, Cornelis MC, Bae SC (2005) Glutathione S-transferase M1, T1, and P1 genotypes and rheumatoid arthritis. J Rheumatol 32: 992-997.

53. Bohanec Grabar P, Logar D, Tomsic M, Rozman B, Dolzan V (2009) Genetic polymorphisms of glutathione S-transferases and disease activity of rheumatoid arthritis. Clin Exp Rheumatol 27: 229-236.

54. Mattey DL, Hutchinson D, Dawes PT, Nixon NB, Clarke S, et al. (2002) Smoking and disease severity in rheumatoid arthritis: association with polymorphism at the glutathione S-transferase M1 locus. Arthritis Rheum 46: 640-646.

55. Kobayashi H, Takeno M, Saito T, Takeda Y, Kirino Y, et al. (2006) Regulatory role of heme oxygenase 1 in inflammation of rheumatoid arthritis. Arthritis Rheum 54: 1132-1142.

56. Keenan BT, Chibnik LB, Cui J, Ding B, Padyukov L, et al. (2010) Effect of interactions of glutathione S-transferase T1, M1, and P1 and HMOX1 gene promoter polymorphisms with heavy smoking on the risk of rheumatoid arthritis. Arthritis Rheum 62: 3196-3210.

57. Yan C, Avadhani NG, Iqbal J (2011) The effects of smoke carcinogens on bone. Curr Osteoporos Rep 9: 202-209.

58. Sloan A, Hussain I, Maqsood M, Eremin O, El-Sheemy M (2010) The effects of smoking on fracture healing. Surgeon 8: 111-116.

59. Rothem DE, Rothem L, Soudry M, Dahan A, Eliakim R (2009) Nicotine modulates bone metabolism-associated gene expression in osteoblast cells. J Bone Miner Metab 27: 555-561.

60. Vo N, Wang D, Sowa G, Witt W, Ngo K, et al. (2011) Differential effects of nicotine and tobacco smoke condensate on human annulus fibrosus cell metabolism. J Orthop Res 29: 1585-1591.

61. Moghaddam A, Zimmermann G, Hammer K, Bruckner T, Grützner PA, et al. (2011) Cigarette smoking influences the clinical and occupational outcome of patients with tibial shaft fractures. Injury 42: 1435-1442.

62. Levin L, Levine J (2010) Cigarette smoking and radiographic alveolar bone height and density. N Y State Dent J 76: 31-35.

63. Xu M, Scott JE, Liu KZ, Bishop HR, Renaud DE, et al. (2008) The influence of nicotine on granulocytic differentiation - inhibition of the oxidative burst and

bacterial killing and increased matrix metalloproteinase-9 release. BMC Cell Biol 9: 19.

64. Kamer AR, El-Ghorab N, Marzec N, Margarone JE 3rd, Dziak R (2006) Nicotine induced proliferation and cytokine release in osteoblastic cells. Int J Mol Med 17: 121-127.

65. Schmal H, Niemeyer P, Südkamp NP, Gerlach U, Dovi-Akue D, et al. (2011) Pain perception in knees with circumscribed cartilage lesions is associated with intra-articular IGF-1 expression. Am J Sports Med 39: 1989-1996.

66. Chen Y, Guo Q, Pan X, Qin L, Zhang P (2011) Smoking and impaired bone healing: will activation of cholinergic anti-inflammatory pathway be the bridge? Int Orthop 35: 1267-1270.

67. Hasnis E, Bar-Shai M, Burbea Z, Reznick AZ (2007) Mechanisms underlying cigarette smoke-induced NF-kappaB activation in human lymphocytes: the role of reactive nitrogen species. J Physiol Pharmacol 58: 275-287.

68. Hasnis E, Bar-Shai M, Burbea Z, Reznick AZ (2007) Cigarette smoke-induced NF-kappaB activation in human lymphocytes: the effect of low and high exposure to gas phase of cigarette smoke. J Physiol Pharmacol 58: 263-274.

69. Hodge S, Matthews G, Mukaro V, Ahern J, Shivam A, et al. (2011) Cigarette smoke-induced changes to alveolar macrophage phenotype and function are improved by treatment with procysteine. Am J Respir Cell Mol Biol 44: 673-681.

70. Meuronen A, Majuri ML, Alenius H, Mäntylä T, Wolff H, et al. (2008) Decreased cytokine and chemokine mRNA expression in bronchoalveolar lavage in asymptomatic smoking subjects. Respiration 75: 450-458.

71. Kane B, Kolsum U, Southworth T, Armstrong J, Woodcock A, et al. (2009) The effects of smoking on the lipopolysaccharide response and glucocorticoid sensitivity of alveolar macrophages of patients with asthma. Chest 136: 163-170.

72. Barbieri SS, Zacchi E, Amadio P, Gianellini S, Mussoni L, et al. (2011) Cytokines present in smokers' serum interact with smoke components to enhance endothelial dysfunction. Cardiovasc Res 90: 475-483.

73. Mortaz E, Lazar Z, Koenderman L, Kraneveld AD, Nijkamp FP, et al. (2009) Cigarette smoke attenuates the production of cytokines by human plasmacytoid dendritic cells and enhances the release of IL-8 in response to TLR-9 stimulation. Respir Res 10: 47.

74. Charlesworth JC, Curran JE, Johnson MP, Göring HH, Dyer TD, et al. (2010) Transcriptomic epidemiology of smoking: the effect of smoking on gene expression in lymphocytes. BMC Med Genomics 3: 29.

75. Nos P, Domènech E (2011) Management of Crohn's disease in smokers: is an alternative approach necessary? World J Gastroenterol 17: 3567-3574.

76. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S (2006) Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc 81: 1462-1471.

77. Bansard C, Lequerré T, Derambure C, Vittecoq O, Hiron M, et al. (2011) Gene profiling predicts rheumatoid arthritis responsiveness to IL-1Ra (anakinra). Rheumatology (Oxford) 50: 283-292.

78. Oei HB, Hooker RS, Cipher DJ, Reimold A (2009) High rates of stopping or switching biological medications in veterans with rheumatoid arthritis. Clin Exp Rheumatol 27: 926-934.

79. Hyrich KL, Watson KD, Silman AJ, Symmons DP (2006) Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 45: 1558-1565.

80. Weinblatt ME, Bingham CO 3rd, Mendelsohn AM, Kim L, Mack M, et al. (2012) Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. Ann Rheum Dis .

81. Greenberg JD, Reed G, Decktor D, Harrold L, Furst D, et al. (2012) A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. Ann Rheum Dis 71: 1134-1142.

82. Ruiz Garcia V, Jobanputra P, Burls A, Cabello JB, Gálvez Muñoz JG, et al. (2011) Certolizumab pegol (CDP870) for rheumatoid arthritis in adults. Cochrane Database Syst Rev 2: CD007649.

83. Abhishek A, Butt S, Gadsby K, Zhang W, Deighton CM (2010) Anti-TNF-alpha agents are less effective for the treatment of rheumatoid arthritis in current smokers. J Clin Rheumatol 16: 15-18.

84. Saevarsdottir S, Wedrén S, Seddighzadeh M, Bengtsson C, Wesley A, et al. (2011) Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. Arthritis Rheum 63: 26-36.

85. Söderlin MK, Petersson IF, Geborek P (2012) The effect of smoking on response and drug survival in rheumatoid arthritis patients treated with their first anti-TNF drug. Scand J Rheumatol 41: 1-9.

86. Lykkesfeldt J, Christen S, Wallock LM, Chang HH, Jacob RA, et al. (2000) Ascorbate is depleted by smoking and repleted by moderate supplementation: a study in male smokers and nonsmokers with matched dietary antioxidant intakes. Am J Clin Nutr 71: 530-536.

87. Vardavas CI, Linardakis MK, Hatzis CM, Malliaraki N, Saris WH, et al. (2008) Smoking status in relation to serum folate and dietary vitamin intake. Tob Induc Dis 4: 8.

88. Gabriel HE, Crott JW, Ghandour H, Dallal GE, Choi SW, et al. (2006) Chronic cigarette smoking is associated with diminished folate status, altered folate form distribution, and increased genetic damage in the buccal mucosa of healthy adults. Am J Clin Nutr 83: 835-841.

89. Xu Z, Vu T, Lee H, Hu C, Ling J, et al. (2009) Population pharmacokinetics of golimumab, an anti-tumor necrosis factor-alpha human monoclonal antibody, in patients with psoriatic arthritis. J Clin Pharmacol 49: 1056-1070.

90. Thaler K, Chandiramani DV, Hansen RA, Gartlehner G (2009) Efficacy and safety of anakinra for the treatment of rheumatoid arthritis: an update of the Oregon Drug Effectiveness Review Project. Biologics 3: 485-498.

91. Navarro-Millán I, Singh JA, Curtis JR (2012) Systematic review of tocilizumab for rheumatoid arthritis: a new biologic agent targeting the interleukin-6 receptor. Clin Ther 34: 788-802.

92. Narvaez J, Díaz-Torné C, Ruiz JM, Hernandez MV, Torrente-Segarra V, et al. (2011) Predictors of response to rituximab in patients with active rheumatoid arthritis and inadequate response to anti-TNF agents or traditional DMARDs. Clin Exp Rheumatol 29: 991-997.

93. Chatzidionysiou K, Lie E, Nasonov E, Lukina G, Hetland ML, et al. (2011) Highest clinical effectiveness of rituximab in autoantibody-positive patients with rheumatoid arthritis and in those for whom no more than one previous TNF antagonist has failed: pooled data from 10 European registries. Ann Rheum Dis 70: 1575-1580.

94. Lal P, Su Z, Holweg CT, Silverman GJ, Schwartzman S, et al. (2011) Inflammation and autoantibody markers identify rheumatoid arthritis patients with enhanced clinical benefit following rituximab treatment. Arthritis Rheum 63: 3681-3691.

95. Cullup H, Middleton PG, Duggan G, Conn JS, Dickinson AM (2004) Environmental factors and not genotype influence the plasma level of interleukin-1 receptor antagonist in normal individuals. Clin Exp Immunol 137: 351-358.

96. Mikuniya T, Nagai S, Tsutsumi T, Morita K, Mio T, et al. (1999) Proinflammatory or regulatory cytokines released from BALF macrophages of healthy smokers. Respiration 66: 419-426.

97. Bartalena L, Manetti L, Tanda ML, Dell'Unto E, Mazzi B, et al. (2000) Soluble interleukin-1 receptor antagonist concentration in patients with Graves' ophthalmopathy is neither related to cigarette smoking nor predictive of subsequent response to glucocorticoids. Clin Endocrinol (Oxf) 52: 647-651.

98. Salvi M, Pedrazzoni M, Girasole G, Giuliani N, Minelli R, et al. (2000) Serum concentrations of proinflammatory cytokines in Graves' disease: effect of treatment, thyroid function, ophthalmopathy and cigarette smoking. Eur J Endocrinol 143: 197-202.

99. Arnson Y, Shoenfeld Y, Amital H (2010) Effects of tobacco smoke on immunity, inflammation and autoimmunity. J Autoimmun 34: J258-265.

100. Shih RH, Lee IT, Hsieh HL, Kou YR, Yang CM (2010) Cigarette smoke extract induces HO-1 expression in mouse cerebral vascular endothelial cells: involvement of c-Src/NADPH oxidase/PDGFR/JAK2/STAT3 pathway. J Cell Physiol 225: 741-750.

101. Reichelt H, Barz D, Thude H (2009) CD34+ and CD133+ Primitive Stem Cell Expression in Peripheral Blood: Considering Gender, Age, and Smoking. Transfusion medicine and hemotherapy: offizielles Organ der Deutschen Gesellschaft fur Transfusionsmedizin und Immunhamatologie 36: 129-134.

102. Chang G, Orav EJ, McNamara T, Tong MY, Antin JH (2004) Depression, cigarette smoking, and hematopoietic stem cell transplantation outcome. Cancer 101: 782-789.

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