Review

One year in review 2016: pathogenesis of rheumatoid arthritis

E. Bellucci[1], R. Terenzi[1], G.M.C. La Paglia[2], S. Gentileschi[3], A. Tripoli[4], C. Tani[4], A. Alunno[2]

[1]*Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Florence, Italy;*
[2]*Rheumatology Unit, Department of Medicine, University of Perugia, Italy;*
[3]*Rheumatology Unit, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Italy;*
[4]*Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy.*

*Eleonora Bellucci, MD**
*Riccardo Terenzi, MD**
Giuliana M.C. La Paglia, MD
Stefano Gentileschi MD
Alessandra Tripoli, MD
Chiara Tani, MD, PhD
Alessia Alunno, MD

**These authors contributed equally to this paper.*

Please address correspondence to:
Riccardo Terenzi, MD,
Rheumatology Unit,
Department of Clinical and Experimental Medicine,
University of Florence,
Viale Pieraccini 18,
50139 Firenze, Italy.
E-mail: terenzi.ricca@gmail.com

Received on July 25, 2016; accepted in revised form on September 1, 2016.

Clin Exp Rheumatol 2016; 34: 793-801.

Key words: rheumatoid arthritis, genetics, T lymphocytes, B lymphocytes, cardiovascular risk

Competing interests: none declared.

ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease characterised by chronic synovial inflammation leading to joint destruction and bone erosions. Although the pathogenic mechanisms underlying the disease are not fully elucidated, it is known that genetic susceptibility and environmental factors trigger an abnormal autoimmune response. Potentially, any organ and tissue could be affected by RA and the increased cardiovascular (CV) risk represents the major complication responsible for a worse prognosis. In this setting, the shared pathogenic mechanisms between RA pathogenesis and accelerated atherosclerosis further strengthen the rationale for a treat-to-target strategy with synthetic and biologic disease modifying anti-rheumatic drugs. The aim of this review is to provide the novel insights, regarding the pathogenesis of RA, published over the last year.

Introduction

Following the previous papers of the "one year in review" collection on rheumatoid arthritis (RA) (1-3), the aim of this review is to provide an overview of the new data emerged on the pathogenesis of RA. We performed a Medline search of English language articles published from the 1st January to 31st December 2015 using MESH terms and free text words for the following search keys: rheumatoid arthritis, genetics, histocompatibility antigens class I, single nucleotide polymorphism, innate immunity, interferon type I, t-lymphocytes, b-lymphocytes, environment, smoking, microbiota, lung, skin, cardiovascular diseases. The most relevant articles were selected for inclusion in this review.

Genetic factors

HLA molecules

In the last few years, knowledge about the role of genetics in the pathogenesis of rheumatoid arthritis (RA) has increased with the discovery of a growing number of genetic loci and single polymorphisms associated with RA susceptibility (4).

Recently, Iwaszko *et al*. demonstrated for the first time that the HLA-E 01:01/01:01 genotype may be associated with reduced risk of RA and may increase the probability of good response to anti-TNF agents. Conversely, the HLA-E 01:03 variant may contribute to a lower probability of achieving disease remission (5). Val and Leu at position 11 in the HLA-DRB1 locus were recently identified as additional susceptibility factors for ACPA-positive RA. Van Steenbergen *et al*. observed that these amino acids are also associated with a more severe disease course and radiographic progression (6). Another study revealed that HLA-DRB1 molecule variants defined by the presence of certain amino acids at positions 11 and 13 displayed the strongest association with the risk of ACPA-positive RA. This finding may be explained at least in part by the fact that the presentation of smoking-induced citrullinated autoantigen may be specifically dependent on the presence of certain amino acid residues at position 13 of the HLA-DRB1 chain (7). Another example of interaction involving HLA-DRB1 was the one detected by Shchetynsky *et al*. concerning the MAP2K4 gene and in particular its single nucleotide polymorphism (SNP) rs10468473. The study suggests that MAP2K4 is an important candidate gene for RA for at least two reasons. First, it increases the risk for ACPA-positive disease in combination with HLA-DRB1 shared epitope (SE) alleles. Secondly, heterozygous individuals for rs10468473 demonstrated higher expression of total MAP2K4 mRNA in the peripheral

blood, compared to A-allele homozygous (8). Focusing on the influence of the HLA region in ACPA – (negative) RA, Bossini-Castillo *et al*. identified that this is linked to a specific position of two amino acids, HLA-B at position 9 and HLADRB1at position 11. In the same study a correlation between increased RA risk and a SNP in the CLYBL gene has been described (9). All the variants of HLA genes known to be associated with an increased risk of RA were combined in a study by Yarwood *et al*. who built the first risk prediction model for the disease. Nevertheless, the predictive performance of this model was rather weak in the general population, but may be used to identify at-risk individuals in suitably designed targeted screening programmes (10).

Lymphocyte activation

B lymphoid kinase (BLK) is a member of the Src family of tyrosine kinases and is associated with RA and several other autoimmune disorders. The BLK risk alleles identified in genome-wide association studies (GWAS) are consistently associated with reduced BLK expression in B cells and B cell lines.. In addition, the BLK risk genotype lowers the threshold for activation of B lymphocytes, and subsequently increases their capacity to interact with T cells and possibly receive T cell help (11). B7-H3 is an important co-stimulatory molecule playing a crucial role in T cell responses. Sun *et al*. found a new B7-H3 SNP (involving a C to T transversion at position 565) associated with RA susceptibility. Of interest, Authors also provided conclusive evidence of an association of B7-H3 and sB7-H3 expression with RA clinical parameters including DAS28 score, disease duration, tender and swollen joint count (12).

Protein citrullination

The human protein tyrosine phosphatase PTPN22 is able to block peptidyl arginine deaminase type 4 (PAD-4) enzyme, thereby preventing protein citrullination. The study performed by Chang *et al*. established a molecular link between PTPN22 and PAD-4 and indicated that the R-to-W (C1858T) conversion of PTPN22 fosters the activation signals in lymphocytes, expands the pool of autoreactive B cells and attenuates TLR-mediated production of type I IFN by myeloid cells, thereby increasing the risk of developing RA (13).

Other

Stark *et al*. have identified a SNP(rs1790834) of cytochrome B5 type A gene (CYB5A) that contributes to the heritable risk in RA women, by decreasing the synthesis of the protein itself and therefore the patient's androgen levels. As a consequence, the risk-lowering minor allele of SNP rs1790834 may help to ensure protective androgen levels in women, whereas the major allele may contribute to low androgen levels, which are insufficient to block development of RA or to ameliorate the inflammatory processes (14).

Kotrych *et al*. detected an increased frequency of CXCL10 (rs8878) G allele carriers among RA patients and additionally associated the GG genotype with extra-articular manifestation (15). Mutations of mannose-binding lectin gene (MBL2) can be involved in complement system dysfunctions with impaired pathogens clearance and resulting in immunological and infectious diseases. A recent meta-analysis performed by Zhang *et al*. demonstrated that a polymorphism of codon 54 in MBL2, may predispose to RA, especially the seropositive or erosive variant of the disease, in East Asian patients. This effect was no longer evident in Caucasian patients and cumulating the two cohorts, revealing a possible race effect. (16) A significant contribution to RA risk is also given by the risk-allele (rs11439060 and rs9138) of the secreted phosphoprotein 1 (SPP1) gene. Gazal *et al*. demonstrated that this allele combination was associated with decreased osteopontin (OPN) serum level, which is associated with ACPA production. Therefore, the influence on the disease risk resulted more important in ACPA-negative RA, and less in ACPA-positive disease (17). Finally, Jines *et al*. explored the functional consequences of a SNP (rs17611) encoding a V802I polymorphism in C5 and proposed a mechanism for its link to RA pathogenesis. They hypothesised that this SNP alters the rate at which elastase generates active C5a in rheumatoid joints, hence recruiting neutrophils to the site of inflammation and maintaining a pro-inflammation environment in target joints (18).

Immunopathogenesis of synovitis

Innate immune response

Despite the central role of the adaptive immune system in RA pathogenesis, the innate immune system has a key role in this scenario. It has been recently demonstrated that patients with active RA have increased expression of nucleotide binding domain and leucin rich pyrin 3 domain (NLRP3) in PB cells. NLRP3 is a sensor protein that leads to constitution of a well-characterised type of inflammasome, the NLRP3-inflammasome. The increased expression of NLRP3 is functionally active in whole blood cells of RA patients and leads to over-expression of IL-1β (19). Furthermore polymorphonuclear cells (PMNs) of RA patients seem to be inherently more reactive to noxious stimuli than healthy PMNs. Indeed, RA PMNs display higher levels of triggering receptor expressed by myeloid cells 1 (TREM1), an activator receptor of PMNs. Activation of TREM1 induces higher secretion of IL-8 and other cytotoxic agents in RA PMNs compared to healthy PMNs (20). Interestingly, higher levels of TREM1 and toll like receptor (TLR) 2 have been found in PBMCS obtained from RA patients with pulmonary involvement with respect to healthy controls, suggesting a possible role for TREM1 and TLR2 in generating pulmonary disease during RA (21). It is now well established that *Porphyromonas gingivalis*-triggered perio-dontitis by is a risk factor for RA. In the last year, it has been discovered that *Porphyromonas gingivalis* enhances articular bone loss by stimulating RANKL in osteoblast via TLR2 (22). In addition, genetic deficiency of Cathepsin K decreases the expression of TLR 4, 5 and 9 resulting in a dramatic reduction of inflammation and bone erosions in experimental RA (23). Another work focused on TLR5 investigating its activity in a mouse model by a direct activation with flagellin.

The activation of TLR5 caused robust osteoclast formation and bone loss via the RANKL pathway. On the contrary, stimulation with flagellin *Tlr 5-/-* mice had no particular effects (24). The secretion of type I interferons (IFNs) is the first cellular reaction to invading pathogens and the first-line response of innate immune system to noxious stimuli. Despite the protective function of these cytokines, an excessive response to their action can contribute to RA pathogenesis. It has been recently discovered that an higher production of IFN is associated with a poor response to rituximab (RTX) therapy but the average IFN level could be modulated by prednisone (25). The evidence that IFN response genes are significantly up-regulated in RA PMNs compared with healthy controls supports a close relationship between the innate immune system and IFN levels in RA (26). In addition, IFN production seems to be deregulated during RA as demonstrated by the functions of Hur protein, an RNA binding protein determining the fate of IFN-mRNA, in fibroblast like synoviocytes (FLS) of RA patients. Reduced expression of Hur severely hampered the type I IFN response in RA FLS (27). Interestingly, some IFN inducible proteins (IFI) like IFI-16 seem to exerts a specific pathologenic role in the development of key clinical features of RA. In fact, RA patients display higher serum levels of IFI-16 and its auto-antibodies (anti-IFI-16 Abs) compared to healthy subjects. The majority of RA patients with detectable circulating IFI-16 protein were also positive for RF and ACPA. Finally the presence of circulating IFI-16 protein, but not of anti- IFI-16-Abs, significantly correlated with RA pulmonary involvement. This correlation was independent of other well-known predictors of RA-associated pulmonary involvement including male gender or smoking habit, suggesting a possible role for IFI-16 in generating RA-associated pulmonary disease (28).

Adaptive immune response

• CD4+ T regulatory and T helper 17 cells

A major role in the pathogenesis of RA has been attributed to the adaptive immune response dysregulation, where regulatory T cells (T reg), effector T cells and antibody-producing B cells are leading actors. As far as Treg cells are concerned, it is now well established that their most specific lineage marker is the forkhead winged helix transcription factor (FoxP3). In this setting, it has been recently reported that methotrexate is able to increase the FoxP3 expression through the demethylation of upstream enhancer of FoxP3 (29). The treatment would lead to a resumption of defective Treg cell suppressive function in DMARD-naive RA patients. The majority of Treg cells isolated from the synovial fluid of RA patients with active arthritis also express another transcription factor called helios (Ikaros transcription factor family) (30). Although the largest subset is represented by helios+ compared to helios- Treg cells, the latter subgroup is characterised by a higher CTLA-4 expression as well as greatest cytokine production (IL-10, IFN-γ, TNF). A common feature between helios subsets was the up-regulation of IL-1R1 although we need further studies to identify its role in the inflammation processes. Takatori *et al*. have shown that helios-mediated suppressive function is closely linked to cell-intrinsic Foxp3 expression in presence of TGF-β in mice (31). However, helios induction seems to be suppressed by IL-6/STAT3 pathway and the treatment with anti-IL-6R antibody (tocilizumab, TCZ) has been reported to increase helios expression in CD4+ T cells in patients with the best clinical response. In this setting, a recent study reported an increased number and improved suppressive function of Treg cells, in the peripheral blood (PB) of RA patients after 52 weeks of treatment with TCZ. Of interest, such increase of Treg cells among CD4+ T cells was directly correlated with disease remission as established by Clinical Disease Activity Index (CDAI) score (32). In recent years, the plasticity of Treg cells towards effector cells and viceversa, is gaining growing scientific interest as possible pathogenic mechanism in RA. Wang *et al*. detected for the first time that IL-17 producing CD4 FoxP3+Tregs cells in PB and synovial fluid of RA patients are increased compared to healthy controls (33). Of interest, unlike in the PB, where IL-17 producing Treg cells seem to preserve their suppressive function, in the SF Treg cells behave as effector T cells acting as Th17 cells, in response to the enriched pro-inflammatory cytokine milieu (TNF-α, IL-1, IL-6) (31). A pro-inflammatory Treg cell phenotype has also been recognised by Zhou *et al*. through a decreased expression of microRNA (miR)-146a and -155 in Treg cells of RA patients (34). In particular, a greater reduction of miR-146a determined an increase expression and activation of STAT-1 correlating with a more active disease and inflammation. In the last year, a novel cytokine called IL-35 has been discovered and it seems to be involved in the enhancing suppressive functions of Treg. Nakano *et al*. have demonstrated a reduced expression of IL-35 in addition to that of Treg cells in the peripheral blood of active RA patients compared to HC (35). However, after treatment with recombinant human IL-35 in vitro it was observed an increased Treg function parallel to a suppressive proliferation cytokines (IL-17 and IFN-γ) and to that effector T cells (35). Recently a new member of the IL-1 cytokine family (IL-37) has been identified to be a potent immune suppressor in the pathogenesis of human RA and in collagen-induced arthritis (CIA) models (36). IL-37 serum levels were higher in RA patients compared to HC suggesting an anti-inflammatory response to the IL-17 and IL-17-driving cytokines. A suppression of the IL-17 axis was achieved with recombinant IL-37 *in vitro*. Van der Geest *et al*. reported that T reg cells accumulate in synovial fluid of RA, show high proliferative activity and a limited apoptosis rate probably related to high transcription levels of anti-apoptotic regulators (Bcl-2 and miR21) (37). These findings are consistent with the aforementioned observations regarding Treg cell plasticity and their propensity to become effector cells. On this basis, a consistent number of studies have suggested the imbalance between Th17/Treg cells as a possible key mechanism in the development and

progression of RA. Guggino *et al*. reported that the treatment with methotrexate and or/methylprednisolone in early RA patients led to a decrease of Th17 cells and a parallel increase of Treg cells and IL-10-producing Th17 cells (38). Unfortunately, such effects were no longer detectable in RA patients with long standing disease suggesting that disease duration may account for irreversible cell modifications from a regulatory to an effector phenotype. Taken the pathogenic role of Th17 cells, the identification of cell types and soluble mediators that are able to modulate their pro-inflammatory activity is intriguing. In this setting, mesenchymal stem cells (MSC) may represent an interesting option. However, recent data highlighted that MSC of RA patients in vitro seem to be unable to downregulate Th17 cells, compared to healthy control (HC), because of their low expression of CCL2 (39). In addition, two recent studies focused on vasoactive intestinal peptide (VIP) and its propensity to convert Th17 pathogenic cells, toward T reg cells in early RA (40, 41).

The CD200/CD200R1 expression and its consequences on RA patients have been explored by Ren *et al*. (42). They found a decreased expression of this pathway in peripheral blood mononuclear cells and CD4+ T cells in RA patients compared to HC, as well as a reduced CD4+ T cells apoptosis, an increased CD4+T cells differentiation toward TH17, an enhancement of Th17 cell-chemotaxis and an improvement of osteoclastogenesis.

• *CD8+ and other T cell subsets*

CD8+ cells play an important role in the induction and maintenance of chronic inflammation. CD8+T cells displaying an effector phenotype, namely CD27-CD62L-CD69+ were found in the PB and SF of RA patients, regardless disease activity, compared to HC (43). Curiously, CD8+ T cells from active RA patients showed the same profile. Interestingly, cytokine production by effector CD8+ cells was lower in patients with disease remission compared to those with active disease. This may suggest that effector CD8+T cells are steadily present in RA PB and SF and modulate the cytokine expression profile in line with disease activity.

Recently a new Th subset called Th9 (able to produce IL-9) has been identified and it has been speculated that Th9 cells may be involved in RA pathogenesis by providing B-cell help thus promoting B cell differentiation, proliferation and antibody production. To clarify the role of Th9 cells in RA, Ciccia *et al*. investigated Th9 cells and IL-9 expression in RA synovial tissue and PB. They observed a consistent proportion of Th9 cells and IL-9 overexpression in RA synovial tissue as well as an increase of Th9 cells in peripheral blood of RA patients (44).

The most recently discovered T cell subpopulation the angiogenic T cells (Tang), may represent an important link between cardiovascular (CV) events and RA. Rodriguez-Carrio *et al*. first demonstrated a lower proportion of circulating Tang cells, compared to HC, establishing a close correlation with risk factors for poor disease prognosis (high activity disease, antibody positivity besides high IFN-α serum levels) (45).

• *Follicular T helper cells, B lymphocytes and B/T cell interaction*

B cell are involved in the pathogenic mechanism trough the regulation of T cell functions, the formation of antibodies directed against citrullinated peptides and the production of pro-inflammatory soluble factors. Besides known autoantigens for ACPA such as self citrullinated proteins, several citrullinated viral, bacterial, fungal and food antigens can lead to the generation of ACPA (46). Indeed, ACPA could cross-reacts with several environmental factors to induce RA trough molecular mimicry. Synovial B cells of RA patients may undergo phenotypic changes with the expression of several molecules that provide them with APC function. The surface-expression profile of molecules involved in antigen presentation and costimulation in synovial B cells of RA patients was compared to patients with psoriatic arthritis (PA) highlighting a different phenotype, which in part could explain the different clinical outcomes after treatment with the anti-CD20 antibody rituximab. In this setting an increased expression of CD86, HLA-DR, HLA-DP, HLA-DQ and a lower expression of CD20 and CD40 was observed by González *et al*. in SF B cells of RA patients (47). Conversely a lower expression of HLA-DP and an increase expression of CD40 was found in PA patients. A shared profile war represented by an up-regulation of CD27 and down-regulation of CD23, all findings that suggest an efficient role as APC.

For the first time Chavele *et al*. have recognised that RA human plasmablasts are potent inducers of follicular T helper cell (Tfh) differentiation through their production of IL-6 (48). Tfh represent a CD4+T cell subset involved in B cell help through the production of IL-21, eventually promoting ectopic lymphoid neogenesis in target tissues. Authors also recognised a positive feedback where Tfh cells, in turn, induce plasmablast formation, through IL-21 production, leading to the development of germinal centers (GCs). As mentioned, IL-21 plays a key role in the differentiation of B cells, class-switch DNA recombination and in GC formation. It has been demonstrated that also CD4+ T cells promote the development of IL-21-producing Tfh cells through an increase of Bcl-3 expression induced by enhanced IL-6/STAT-3 signaling (49). Recently, a clinical trial showed the selective involvement of IL-21 in the phosphorylation and nuclear translocation of STAT-1 leading to B cell differentiation (50). All these events seem to be regulated by Bruton tyrosine Kinase (Btk) whose activation, namely phosphorilation, significantly correlates with rheumatoid factor (RF) titers in RA patients. In the last years the discovery of Btk expression in synovial tissue macrophages and its pro-inflammatory effects in RA provided new clue for its possible pathogenic role in RA (51).

On this basis, B -T cell interaction represents a pathogenic aspect worth to be targeted for therapeutic purposes. In this regard, the CTLA-4 Ig Abatacept was found able to reduce Tfh cells and the phosphorylation of Syk (pSyk) in peripheral blood B cell of RA patients (52). The highest levels of pSyk in RA

patients seemed to correlate with a major production of ACPA (52).

In an elegant murine model of proteoglycan induced arthritis (PGIA) it has been observed that a B-cell derived IFN-γ production was able to induce arthritis while mice with B-cell-specific IFN-γ deficiency were resistant to the development of PGIA (53). B cell depletion lead to an increase in the differentiation of CD4+ T cells into T reg cells and surprisingly IFN-γ-producing-CD4+T cells did not contribute to the increase of T reg cells.

A model of RA pathogenesis in which T reg cells show intrinsic defects and B cells develop resistance to their suppression was set up by Rapetti *et al*. (54). A control mechanism by which regulatory T cells suppress expansion, pro-inflammatory cytokine and antibody production of B cell, has been already recognised in Fas-mediated apoptosis. RA patients showed a loss of T reg suppression, in contrast to HC, probably due not only to impaired T reg cells but also to B cell resistance trough both reduced Fas expression and reduced internalisation/signalling.

In addition to the B cells functions described above, increasing evidence support the involvement of B cells in bone resorption and osteoclastogenesis. A pro-inflammatory B cell subset responsible for RANKL and TNF-α production has been identified by the expression of FcRL4 (55). Since this cell subset expresses high levels of mRNA for RANKL and TNF-α, it is probably involved in bone erosion. Similar findings were obtained by Engelmann *et al*. who demonstrated a significant correlation between CD5+ B cells and serum levels of carboxy-terminal collagen crosslinks (CTX-1), a marker of bone turnover (56). Finally, not only B cells but also NKT cells may be involved in bone destruction occurring in RA patients. The addition of α-galactosylceramide (αGalCer) to HC PB mononuclear cells *in vitro,* led to an inhibition of osteoclastogenesis through the NKT response (57). Conversely, a dysfunction of NKT in RA patients lead to a decrease of inflammatory bone destruction mediated by αGalCer.

Beyond the joint

Extra-articular manifestations

• *Environment*

Cigarette smoking is the most established environmental risk factor for RA, mainly among subjects positive for ACPA and/or RF. Several studies have identified significant interactions between smoking and SE alleles for susceptibility to seropositive RA. HLA-SE positive individuals were more frequently positive for ACPA compared with HLA-SE negative individuals prior to the onset of symptoms of RA, particularly for antibodies against CEP-1 and Fibβ62-81a. HLA-SE and smoking showed increased association to the presence of the antibodies closer to disease onset (58).

A Malaysian study demonstrated for the first time that occupational exposure to textile dust was associated with an increased risk of ACPA-positive and ACPA-negative RA. Additionally HLA-DRB1 SE-positive individuals exposed to textile dust had a high risk of developing ACPA-positive RA. The significant gene–environment interaction between HLA-DRB1 SE and textile dust can support the hypothesis that various lung exposures may play an important role in the aetiology of RA (59). Viral or bacterial infections may also trigger the disease onset. It is well known that RA patients are at higher risk of developing TB than the general population because of treatment-related immunosuppression. But a population-based study for the first time also investigated the association between prior TB and the risk of RA. In this study, TB was much more prevalent in RA patients than in control subjects (60).

• *Microbiota*

Recent studies have highlighted the potential influence of the mucosal microbiome on RA onset and progression. Zhang *et al*. found that there is microbiome divergence between RA patients and healthy control in feces, salivary and dental samples. In particular, they recorded a depletion in Haemophilus species and an overrepresentation of Lactobacillus salivarius in RA patients compared with healthy subjects. They show that these imbalances can be partially redressed by disease-modifying anti-rheumatic drugs (DMARDs) (61).

Porphyromonas gengivalis is considered one of the most important bacteria implicated in chronic peridontal disease because of its capability to transform arginine into citrulline. However, a recent study did not confirm any association between anti–Porphyromonas gingivalis antibodies and RA or ACPA status in a large cohort of patients with early RA. These results suggest that the association of periodontitis and RA could be linked to other bacterial species than *P gingivalis* or to a mechanism other than citrullination (62).

•*Lung*

Lungs might be the initial site of autoantibody production. Citrullination refers to the conversion of arginine residues to citrulline residues, a post-translational process catalysed by an enzyme family called peptidylarginine deiminases (PADs). A recent study demonstrated for the first time that in broncho-alveolar lavage of smoker subjects there was increased PAD2 levels compared to non-smokers (63) and another study has recently confirmed this finding in patients with early untreated RA (64). The lungs are even the most common site of extra-articular involvement. RA-related interstitial lung disease (RA-ILD) is identified in up to 60% of patients and significantly contributes to the morbidity and mortality. Several studies have suggested that genetic factors, environmental exposure such as tobacco, and some drugs can be implicated in the development of RA-ILD, but the exact mechanisms underlying RA-ILD are still unknown. In a retrospective cohort of 246 RA patients the risk of pulmonary involvement in RA was higher in males, elderly patients, patients with a history of tobacco smoke exposure, RF-positive and patients with a history of exposure to azathioprine (65). The role of tobacco in RA-related ILD and the relationship with HLA–DRB1 SE was also confirmed by another study (66). The same authors also showed that higher ACPA titers are more strongly associated with ILD; moreover, ACPA seem to be markers of severity and extent of RA-ILD (67). In a recent study,

higher levels of matrix metalloproteinase (MMP)-7 and interferon-γ -inducible protein 10 (IP-10/CXCL10) were found in the serum of a cohort of patients with RA and ILD (68). Moreover, a recent study demonstrated a significant decrease in CD19+Foxp3+ Bregs in RA patients with or without ILD as compared to healthy controls, as well as a reduction of CD19+TGFβ+ Bregs in RA patients with ILD. These data suggest that CD19+TGFβ+ Bregs might play an important role not only in the pathogenesis of RA, but also in in pulmonary damage (69).

Recently, high resolution computed tomography (HRCT) studies of the lungs demonstrated an increased prevalence of subclinical airway abnormalities consistent with bronchiectasis at disease diagnosis in RA patients, supporting the hypothesis that bronchiectasis typically precedes RA and that it could play a role in the disease development. Indeed, bronchiectasis may induce and exacerbate autoimmunity response in RA by bacterial infection in the lung as suggested by two recent studies (70, 71). In both studies is observed an increased prevalence and titers of both ACPAs and RF in patients with BR/RA compared with RA controls. Perry *et al*. demonstrated even that the group of patients with RA and co-existent BR had high levels of RA disease activity, severity and RA autoantibodies spite of little tobacco exposure; suggesting that other factors, different from tobacco, must drive the very high levels of anti-CCP positivity (71).

Cardiovascular risk

It is now well established that RA patients have an increased risk of cardiovascular (CV) events compared to the general population. These comorbidities are intrinsically related to higher CV mortality that to date is the most common cause of death in RA (72).

This risk has been correlated to traditional CV risk factors but also to several RA-related factors the latter contributing to the development of CV after adjustment for traditional CV factors.

Among RA- related factors, it has been recently demonstrated that a reduction of disease activity, as assessed with CDAI, was associated with reduced CV risk, independently of immunomodulatory treatments (73). In addition, data from the CARMA Project (CARdiovascular in rheuMAtology) revealed that HAQ seems to be independently associated to the occurrence of CV events in RA (74).

These findings underline the burden of functional disease status, similarly to higher levels of personal health stress and depressive symptoms that are associated with subclinical measures of atherosclerosis (coronary artery calcium and carotid intima-media thickness) in RA patients (75).

Indeed, the risk prediction scores developed for the general population have been also applied to RA patients in several studies but it has been demonstrated that risk algorithms understimate the true CV risk in these patients (76-78). Therefore, both tight control of the disease activity and adequate CV risk stratification should be carried out in patients with RA to minimise the increased risk of CV death. A disease-specific risk score for CV outcomes in RA (ERS-RA) was developed to improves the classification risk based on a large prospectively collected cohort of US-based RA registry (CORRONA) (77).

Chronic inflammation seems to play the most important role in increased CV morbidity with disease duration being a key factor. Indeed, a recent nationwide study suggests that patients with recent-onset RA who receive consistent RA medication have no increased risk for CV mortality compared to the general population, at least in the early years of the disease. (79)

On the contrary, other data suggest that patients with early arthritis have an increased cardiovascular risk and an increased prevalence of some comorbidities such as arterial hypertension and dyslipidaemia with respect to the general population (80). Conversely, another study hypothesised that the development of premature atherosclerosis in early stage of RA reflects a much longer period of subclinical inflammation which leads to endothelial activation and dysfunction as well as increased accumulation of advanced glycation end products (AGEs). AGEs can ligate to the their receptor RAGE on endothelial cell, resulting in endothelial activation e formation of the soluble vascular cellular activation molecule 1 (sVCAM-1). In this study the endothelial function of newly diagnosed RA patients, reflected by measurement of small artery elasticity (SAE), was found to be decreased in contrast to the normal intima-media thickness (IMT), suggesting long-standing pro-atherosclerotic events already present in early stages of disease (81). The ultrasound measurement of IMT has been evaluated by several studies as a marker of atherosclerosis progression and, therefore, as a CV risk factor predictor (82). In fact, the increase of IMT appears correlated with higher ESR confirming the fundamental role played by inflammation in the development of atherosclerosis in RA. The evaluation of the impact of RA *per se* on arterial disease showed that in absence of classical CV risk factors (hypertension, diabetes, dyslipidaemia and smoking), RA is sufficient to cause atheromatosis but not alterations of arterial elasticity or hypertrophy. In addition, according to the aforementioned studies, while accelerated atheromatosis is proven during the first 5 years after disease onset, preclinical atheromatosis appears earlier in the disease course and seems to be independent of FR and anti-CCP positivity, but associated with disease activity expressed by DAS28 (83). As far as the lipid profile is concerned, its association with the pathogenesis of atherosclerosis and CVD in RA is still controversial. It is recognised that the absolute lipid concentrations are modified in RA as a result of the active inflammatory state, leading to an increased CV risk It is well established that DMARDs decreases CV morbidity and mortality, and a recent study comparing different DMARDs in light of subclinical atherosclerosis found a beneficial and comparable effect of MTX >20 mg/wk and biologics (anti-TNF-α on reducing markers of atherosclerosis. A novel positive influence was found also for cyclosporine A, conversely other synthetic DMARDs recommended in RA (leflunomide, sulphsalazine) showed no effect on IMT and presence of plaques (84). Regarding biologic therapy, toci-

lizumab (TCZ) deservers a closer attention in relation to its burden on changing the lipid profile. McInnes *et al*. in a randomised, placebo-controlled study (85) reported that TCZ in RA patients not only reduced markers of inflammation but also affected CV risk, revising quantitative e qualitative aspect of lipids and lipoproteins, Such changes included global increase of LDL and triglycerid but normalisation of small LDL particle concentration considered more proatherogenic. Favourable remodelling of HDL particles with increase of small HDL that have an anti-inflammatory phenotype and reduction of medium and related-SSA HDL representatives of pro-infiammatory status has been observed. Taken together, all the available studies point out that accelerated atherosclerosis is a key event paralleling disease pathogenesis and depend on that; as a consequence, the adoption of a treat-to-target strategy in RA may be beneficial not only because of the improvement in pain and function, but also because of a reduction in CV risk.

Conclusions

The studies performed in the last year confirmed that RA is a multifactorial disease and its pathogenic mechanisms are still poorly understood. The correlations among the genetic and environmental risks factor with the immune system still represent a great challenge for further investigation.

References

1. CALABRÒ A, CATERINO AL, ELEFANTE E *et al*.: One year in review 2016: novelties in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2016; 34: 357-72.
2. PICERNO V, FERRO F, ADINOLFI A, VALENTINI E, TANI C, ALUNNO A: One year in review: the pathogenesis of rheumatoid arthritis. *Clin Exp Rheumatol* 2015; 33: 551-8
3. GUIDELLI GM, BARSKOVA T, BRIZI MG *et al*.:One year in review: novelties in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2015; 33: 102-8.
4. SUZUKI A, YAMAMOTO K: From genetics to functional insights into rheumatoid arthritis. *Clin Exp Rheumatol* 2015; 33 (Suppl 92): S40-3.
5. IWASZKO M, ŚWIERKOT J, KOLOSSA K, JEKA S, WILAND P, BOGUNIA-KUBIK K: Polymorphisms within the human leucocyte antigen-E gene and their associations with susceptibility to rheumatoid arthritis as well as clinical outcome of anti-tumor necrosis factor therapy. *Clin Exp Immunol* 2015; 182: 270-7.
6. VAN STEENBERGEN HW, RAYCHAUDHURI S, RODRÍGUEZ-RODRÍGUEZ L *et al*.: Association of valine and leucine at HLA-DRB1 position 11 with radiographic progression in rheumatoid arthritis, independent of the shared epitope alleles but not independent of anti-citrullinated protein antibodies. *Arthritis Rheumatol* 2015; 67: 877-86.
7. KIM K, JIANG X, CUI J *et al*.: Interactions between amino acid-defined major histocompatibility complex class II variants and smoking in seropositive rheumatoid arthritis. *Arthritis Rheumatol* 2015; 67: 2611-23.
8. BOSSINI-CASTILLO L, DE KOVEL C, KALLBERG H *et al*.: A genome-wide association study of rheumatoid arthritis without antibodies against citrullinated peptides. *Ann Rheum Dis* 2015; 74: e15.
9. LIU J, ZHU L, XIE G, BAO J, YU Q: Let-7 miRNAs Modulate the Activation of NF-κB by Targeting TNFAIP3 and Are Involved in the Pathogenesis of Lupus Nephritis. *PloS One* 2015; 10: e0121256.
10. YARWOOD A, HAN B, RAYCHAUDHURI S *et al*.: (Rheumatoid Arthritis Consortium International (RACI), WORTHINGTON J, BARTON A, EYRE S) A weighted genetic risk score using all known susceptibility variants to estimate rheumatoid arthritis risk. *Ann Rheum Dis* 2015; 74: 170-6.
11. SIMPFENDORFER KR, ARMSTEAD BE, SHIH A *et al*.: Autoimmune disease-associated haplotypes of BLK exhibit lowered thresholds for B cell activation and expansion of Ig class-switched B cells. *Arthritis Rheumatol* 2015; 67: 2866-76.
12. SUN J, LIU C, GAO L *et al*.: Correlation between B7-H3 expression and rheumatoid arthritis: A new polymorphism haplotype is associated with increased disease risk. *Clin Immunol* 2015; 159: 23-32.
13. CHANG HH, DWIVEDI N, NICHOLAS AP, HO IC: The W620 Polymorphism in PTPN22 Disrupts Its Interaction With Peptidylarginine Deiminase Type 4 and Enhances Citrullination and NETosis. *Arthritis Rheumatol* 2015; 67: 2323-34.
14. STARK K, STRAUB RH, ROVENSKÝ J, BLAŽIČKOVÁ S, EISELT G, SCHMIDT M: CYB5A polymorphism increases androgens and reduces risk of rheumatoid arthritis in women. *Arthritis Res Ther* 2015; 17: 56.
15. KOTRYCH D, DZIEDZIEJKO V, SAFRANOW K, DROZDZIK M, PAWLIK A: CXCL9 and CXCL10 gene polymorphisms in patients with rheumatoid arthritis. *Rheumatol Int* 2015; 35: 1319-23.
16. ZHANG C, ZHU J, LI SL, WANG H, ZHU QX: The association of mannose-binding lectin genetic polymorphisms with the risk of rheumatoid arthritis: a meta-analysis. *J Recept Signal Transduct Res* 2015; 35: 357-62.
17. KAWASAKI A, NICAISE P, AMOS C *et al*.: Identification of secreted phosphoprotein 1 gene as a new rheumatoid arthritis susceptibility gene. *Ann Rheum Dis* 2015; 74: e19.
18. GILES JL, CHOY E, VAN DEN BERG C, MORGAN BP, HARRIS CL: Functional analysis of a complement polymorphism (rs17611) associated with rheumatoid arthritis. *J Immunol* 2015; 194: 3029-34.
19. CHOULAKI C, PAPADAKI G, REPA A *et al*.: Enhanced activity of NLRP3 inflammasome in peripheral blood cells of patients with active rheumatoid arthritis. *Arthritis Res Ther* 2015;17: 257.
20. CHEN X, EKSIOGLU EA, CARTER JD *et al*.: Inactivation of DAP12 in PMN inhibits TREM1-mediated activation in rheumatoid arthritis. *PLoS One* 2015; 10: e0115116.
21. PAPANIKOLAOU IC, BOKI KA, GIAMARELLOS-BOURBOULIS EJ *et al*.: Innate immunity alterations in idiopathic interstitial pneumonias and rheumatoid arthritis-associated-interstitial lung diseases. *Immunol Lett* 2015; 163: 179-86.
22. KASSEM A, HENNING P, LUNDBERG P, SOUZA PP, LINDHOLM C, LERNER UH: Porphyromonas gingivalis stimulates bone resorption by enhancing RANKL (receptor activator of NF-κB ligand) through activation of Toll-like receptor 2 in osteoblasts. *J Biol Chem* 2015; 290: 20147-58.
23. HAO L, ZHU G, LU Y *et al*.: Deficiency of cathepsin K prevents inflammation and bone erosion in rheumatoid arthritis and periodontitis and reveals its shared osteoimmune role. *FEBS Lett* 2015; 589: 1331-9.
24. KASSEM A, HENNING P, KINDLUND B, LINDHOLM C, LERNER UH: TLR5, a novel mediator of innate immunity-induced osteoclastogenesis and bone loss. *FASEB J* 2015; 29: 4449-60.
25. DE JONG TD, VOSSLAMBER S, BLITS M *et al*.: Effect of prednisone on type I interferon signature in rheumatoid arthritis: consequences for response prediction to rituximab. *Arthritis Res Ther* 2015; 17: 78.
26. WRIGHT HL, THOMAS HB, MOOTS RJ, EDWARDS SW: Interferon gene expression signature in rheumatoid arthritis neutrophils correlates with a good response to TNFi therapy. *Rheumatology* (Oxford) 2015; 54: 188-93.
27. HERDY B, KARONITSCH T, VLADIMER GI *et al*.: The RNA-binding protein HuR/ELAVL1 regulates IFN-β mRNA abundance and the type I IFN response. *Eur J Immunol* 2015; 45: 1500-11.
28. ALUNNO A, CANEPARO V, BISTONI O *et al*.: Circulating interferon-inducible protein IFI16 correlates with clinical and serological features in rheumatoid arthritis. *Arthritis Care Res* (Hoboken). 2016; 68: 440-5.
29. CRIBBS AP, KENNEDY A, PENN H, AMJADI P *et al*.: Methotrexate restores regulatory t cell function through demethylation of the FoxP3 upstream enhancer in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2015; 67: 1182-92.
30. MÜLLER M, HERRATH J, MALMSTRÖM V: IL-1R1 is expressed on both Helios(+) and Helios(-) FoxP3(+) CD4(+) T cells in the rheumatic joint. *Clin Exp Immunol* 2015; 182: 90-100.
31. TAKATORI H, KAWASHIMA H, MATSUKI A *et al*.: Helios enhances treg cell function in cooperation with FoxP3. *Arthritis Rheumatol* 2015; 67: 1491-502.
32. CHAVELE KM, MERRY E, EHRENSTEIN MR: Cutting edge: circulating plasmablasts induce the differentiation of human T follicular helper cells via IL-6 production. *J Immunol* 2015; 194: 248.

33. WANG T, SUN X, ZHAO J *et al*.: Regulatory T cells in rheumatoid arthritis showed increased plasticity toward Th17 but retained suppressive function in peripheral blood. *Ann Rheum Dis* 2015; 74: 1293-301.
34. ZHOU Q, HAUPT S, KREUZER JT *et al*.: Decreased expression of miR-146a and miR-155 contributes to an abnormal Treg phenotype in patients with rheumatoid arthritis. *Ann Rheum Dis* 2015; 74: 1265-74.
35. NAKANO S, MORIMOTO S, SUZUKI S *et al*.: Immunoregulatory role of IL-35 in T cells of patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2015; 54: 1498-506.
36. YE L, JIANG B, DENG J *et al*.: IL-37 alleviates rheumatoid arthritis by suppressing IL-17 and IL-17-triggering cytokine production and limiting Th17 cell proliferation. *J Immunol* 2015; 194: 5110-9.
37. VAN DER GEEST KS, SMIGIELSKA-CZEPIEL K, PARK JA *et al*.: SF Treg cells transcribing high levels of Bcl-2 and microRNA-21 demonstrate limited apoptosis in RA. *Rheumatology* (Oxford) 2015; 54: 950-8.
38. WU C, GOODALL JC, BUSCH R *et al*.: Relationship of CD146 expression to secretion of interleukin (IL)-17, IL-22 and interferon-γ by CD4(+) T cells in patients with inflammatory arthritis. *Clin Exp Immunol* 2015; 179: 378-91.
39. SUN Y, DENG W, GENG L *et al*.: Mesenchymal stem cells from patients with rheumatoid arthritis display impaired function in inhibiting Th17 cells. *J Immunol Res* 2015; 2015: 284215.
40. JIMENO R, LECETA J, GARÍN M *et al*.: Th17 polarization of memory Th cells in early arthritis: the vasoactive intestinal peptide effect. *J Leukoc Biol* 2015; 98: 257-69.
41. JIMENO R, GOMARIZ RP, GARÍN M *et al*.: The pathogenic Th profile of human activated memory Th cells in early rheumatoid arthritis can be modulated by VIP. *J Mol Med* (Berl). 2015; 93: 457-67.
42. REN Y, YANG B, YIN Y *et al*.: Aberrant CD200/CD200R1 expression and its potential role in Th17 cell differentiation, chemotaxis and osteoclastogenesis in rheumatoid arthritis. *Rheumatology* (Oxford). 2015; 54: 712-21.
43. CARVALHEIRO H, DUARTE C, SILVA-CARDOSO S *et al*.: CD8+ T cell profiles in patients with rheumatoid arthritis and their relationship to disease activity. *Arthritis Rheumatol* 2015; 67: 363-71.
44. CICCIA F, GUGGINO G, RIZZO A *et al*.: Potential involvement of IL-9 and Th9 cells in the pathogenesis of rheumatoid arthritis. *Rheumatology* (Oxford) 2015; 54: 2264-72.
45. RODRÍGUEZ-CARRIO J, ALPERI-LÓPEZ M, LÓPEZ *et al*.: Angiogenic T cells are decreased in rheumatoid arthritis patients. *Ann Rheum Dis* 2015; 74: 921-7.
46. TSUDA R, OZAWA T, KOBAYASHI E: Monoclonal antibody against citrullinated peptides obtained from rheumatoid arthritis patients reacts with numerous citrullinated microbial and food proteins. *Arthritis Rheumatol* 2015; 67: 202.
47. ARMAS-GONZÁLEZ E, DÍAZ-MARTÍN A, DOMÍNGUEZ-LUIS MJ : Differential antigen-presenting B cell phenotypes from synovial microenvironment of patients with rheumatoid and psoriatic arthritis. *J Rheumatol* 2015; 42: 1825-34.
48. CHAVELE KM, MERRY E, EHRENSTEIN MR: Cutting edge: circulating plasmablasts induce the differentiation of human T follicular helper cells via IL-6 production. *J Immunol* 2015; 194: 24.
49. MEGURO K, SUZUKI K, HOSOKAWA J *et al*.: Role of Bcl-3 in the development of follicular helper T cells and in the pathogenesis of rheumatoid arthritis. *Arthritis Rheumatol* 2015; 67: 2651-60.
50. WANG SP, IWATA S, NAKAYAMADA S *et al*.: Amplification of IL-21 signalling pathway through Bruton's tyrosine kinase in human B cell activation. *Rheumatology* (Oxford) 2015; 54: 1488-97.
51. HARTKAMP LM, FINE JS, VAN ES IE *et al*.: Btk inhibition suppresses agonist-induced human macrophage activation and inflammatory gene expression in RA synovial tissue explants. *Ann Rheum Dis* 2015; 74: 1603-11.
52. IWATA S, NAKAYAMADA S, FUKUYO S *et al*.: Activation of Syk in peripheral blood B cells in patients with rheumatoid arthritis: a potential target for abatacept therapy. *Arthritis Rheumatol* 2015; 67: 63-73.
53. OLALEKAN SA, CAO Y, HAMEL KM *et al*.: B cells expressing IFN-γ suppress Treg-cell differentiation and promote autoimmune experimental arthritis. *Eur J Immunol* 2015; 45: 988-98.
54. RAPETTI L, CHAVELE KM, EVANS CM *et al*.: B cell resistance to Fas-mediated apoptosis contributes to their ineffective control by regulatory T cells in rheumatoid arthritis. *Ann Rheum Dis* 2015; 74: 294-302.
55. YEO L, LOM H, JUAREZ M *et al*.: Expression of FcRL4 defines a pro-inflammatory, RANKL-producing B cell subset in rheumatoid arthritis. *Ann Rheum Dis* 2015; 74: 928-35.
56. ENGELMANN R, WANG N, KNEITZ C *et al*.: Bone resorption correlates with the frequency of CD5+ B cells in the blood of patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2015; 54: 545-53.
57. JIN HM, KEE SJ, CHO YN *et al*.: Dysregulated osteoclastogenesis is related to natural killer T cell dysfunction in rheumatoid arthritis. *Arthritis Rheumatol* 2015; 67: 2639-50.
58. KOKKONEN H, BRINK M, HANSSON M *et al*.: Associations of antibodies against citrullinated peptides with human leukocyte antigen-shared epitope and smoking prior to the development of rheumatoid arthritis. *Arthritis Res Ther* 2015; 17: 125.
59. TOO CL, MUHAMAD NA, ILAR A *et al*.: MyEIRA Study Group. Occupational exposure to textile dust increases the risk of rheumatoid arthritis: results from a Malaysian population-based case-control study. *Ann Rheum Dis* 2016; 75: 997-1002.
60. SHEN TC, LIN CL, WEI CC *et al*.: Previous history of tuberculosis is associated with rheumatoid arthritis. *Int J Tuberc Lung Dis* 2015; 19: 1401-5.
61. ZHANG X, ZHANG D, JIA H *et al*.: The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. *Nat Med* 2015; 21: 895-905.
62. KIM K, JIANG X, CUI J *et al*.: Interactions between amino acid-defined major histocompatibility complex class II variants and smoking in seropositive rheumatoid arthritis. *Arthritis Rheumatol* 2015; 67: 2611-23.
63. DAMGAARD D, FRIBERG BRUUN NIELSEN M, QUISGAARD GAUNSBAEK M, PALARASAH Y, SVANE-KNUDSEN V, NIELSEN CH: Smoking is associated with increased levels of extracellular peptidylarginine deiminase 2 (PAD2) in the lungs. *Clin Exp Rheumatol* 2015; 33: 405-8.
64. REYNISDOTTIR G, OLSEN H, JOSHUA V *et al*.: Signs of immune activation and local inflammation are present in the bronchial tissue of patients with untreated early rheumatoid arthritis. *Ann Rheum Dis* 2016; 75: 1722-7.
65. KAWASSAKI AM, PEREIRA DA, KAY FU, LAURINDO IM, CARVALHO CR, KAIRALLA RA: Pulmonary involvement in rheumatoid arthritis: evaluation by radiography and spirometry. *J Bras Pneumol* 2015; 41: 331-42.
66. RESTREPO JF, DEL RINCÓN I, BATTAFARANO DF, HAAS RW, DORIA M, ESCALANTE A: Clinical and laboratory factors associated with interstitial lung disease in rheumatoid arthritis. *Clin Rheumatol* 2015; 34: 1529-36.
67. ROCHA-MUÑOZ AD, PONCE-GUARNEROS M, GAMEZ-NAVA JI *et al*.: Anti-cyclic citrullinated peptide antibodies and severity of interstitial lung disease in women with rheumatoid arthritis. *J Immunol Res* 2015; 2015: 151626.
68. CHEN J, DOYLE TJ, LIU Y *et al*.: Biomarkers of rheumatoid arthritis-associated interstitial lung disease. *Arthritis Rheumatol* 2015; 67: 28-38.
69. GUO Y, ZHANG X, QIN M, WANG X: Changes in peripheral CD19(+)Foxp3(+) and CD19(+) TGFβ(+) regulatory B cell populations in rheumatoid arthritis patients with interstitial lung disease. *J Thorac Dis* 2015; 7: 471-7.
70. QUIRKE AM, PERRY E, CARTWRIGHT A *et al*.: Bronchiectasis is a model for chronic bacterial infection inducing autoimmunity in rheumatoid arthritis. *Arthritis Rheumatol* 2015; 67: 2335-42.
71. PERRY E, EGGLETON P, DE SOYZA A, HUTCHINSON D, KELLY C: Increased disease activity, severity and autoantibody positivity in rheumatoid arthritis patients with co-existent bronchiectasis. *Int J Rheum Dis* 2015 Jul 22 [Epub ahead of print].
72. PINHEIRO, FA, SOUZA DC, SATO EI: A study of multiple causes of death in rheumatoid arthritis. *J Rheumatol* 2015; 42: 2221-8.
73. SOLOMON DH, REED GW, KREMER JM *et al*.: Disease activity in rheumatoid arthritis and the risk of cardiovascular events. *Arthritis Rheumatol* 2015: 67: 1449-55.
74. CASTAÑEDA S, MARTÍN-MARTÍNEZ MA, GONZÁLEZ-JUANATEY C *et al*.: Cardiovascular morbidity and associated risk factors in Spanish patients with chronic inflammatory rheumatic diseases attending rheumatology clinics: Baseline data of the CARMA Project. *Semin Arthritis Rheum* 2015; 44: 618-26.
75. LIU YL, SZKLO M, DAVIDSON KW, BATHON JM, GILES JT: Differential association of psychosocial comorbidities with subclinical atherosclerosis in rheumatoid arthritis. *Arthritis*

Care Res (Hoboken) 2015; 67: 1335-44.
76. ARTS EE, POPA C, DEN BROEDER AA *et al*.: Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. *Ann Rheum Dis* 2015; 74: 668-74.
77. SOLOMON DH, GREENBERG J, CURTIS JR *et al*.: Derivation and internal validation of an expanded cardiovascular risk prediction score for rheumatoid arthritis: a Consortium of Rheumatology Researchers of North America Registry Study. *Arthritis Rheumatol* 2015; 67: 1995-2003.
78. CORRALES A, DESSEIN PH, TSANG L *et al*.: Carotid artery plaque in women with rheumatoid arthritis and low estimated cardiovascular disease risk: a cross-sectional study. *Arthritis Res Ther* 2015; 17: 55.
79. KEROLA AM, NIEMINEN TV, VIRTA LJ *et al*.: No increased cardiovascular mortality among early rheumatoid arthritis patients: a nationwide register study in 2000-2008. *Clin Exp Rheumatol* 2015; 33: 391-8.
80. GHERGHE AM, DOUGADOS M, COMBE B *et al*.: Cardiovascular and selected comorbidities in early arthritis and early spondyloarthritis, a comparative study: results from the ESPOIR and DESIR cohorts. *RMD Open* 2015; 1: e000128.
81. DE GROOT L, JAGER NA, WESTRA J *et al*.: Does reduction of disease activity improve early markers of cardiovascular disease in newly diagnosed rheumatoid arthritis patients? *Rheumatology* (Oxford) 2015; 54: 1257-61.
82. DEL RINCÓN I, POLAK JF, O'LEARY DH *et al*.: Systemic inflammation and cardiovascular risk factors predict rapid progression of atherosclerosis in rheumatoid arthritis. *Ann Rheum Dis* 2015; 74: 1118-23.
83. ARIDA A, ZAMPELI E, KONSTANTONIS G *et al*.: Rheumatoid arthritis is sufficient to cause atheromatosis but not arterial stiffness or hypertrophy in the absence of classical cardiovascular risk factors. *Clin Rheumatol* 2015; 34: 853-9.
84. KISIEL B, KRUSZEWSKI R, JUSZKIEWICZ A *et al*.: Methotrexate, cyclosporine a, and biologics protect against atherosclerosis in rheumatoid arthritis. *J Immunol Res* 2015; 2015: 759610.
85. MCINNES IB, THOMPSON L, GILES JT *et al*.: Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. *Ann Rheum Dis* 2015; 74: 694-702.