

Bulletin Board

New study reveals disability in rheumatoid arthritis patients is in decline

Study validates the decline in disability in the pre-DMARD period has continued in the biologic era.

In a new study recently published online in *Annals of the Rheumatic Diseases*, disability in rheumatoid arthritis (RA) was shown to decrease an average of 1.7% per year since the introduction of disease-modifying antirheumatic drugs (DMARDs) to the treatment armamentarium.

According to one of the study investigators, Eswar Krishnan, Division of Rheumatology and Immunology at Stanford University (CA, USA), the finding justifies “continued emphasis on early and consistent [DMARDs] use and the incorporation of biologicals into our therapeutic repertoire.”

A total of 4651 adult patients from the national longitudinal database Arthritis, Rheumatism and Aging Medical Information System (ARAMIS) were evaluated in the study. The majority of patients enrolled were females (76%) and nearly all were white (88%).

Patients included in the study were each mailed a Health Assessment Questionnaire (HAQ), every 6 months spanning from 1983 through to 2006. The HAQ was designed to assess disability on a scale of 0–3 (with 3 being the worst) in a wide range of areas including arising, eating and walking.

The study investigators found that the average HAQ-disability score improved from 1.3 in the 1980’s to 1.2 in the 1990’s and to ≤ 1.1 in the 2000’s. The study period was then divided up into three defined areas: the ‘NSAID-based’ era from 1982–1990, the ‘Methotrexate (MTX)/DMARD’ era from 1991–2000 and the ‘MTX and biologic DMARD’ period from 2001–2006.

Having plotted the data on a graph using the least-squares regression, it became

apparent to the investigators that disability remained relatively constant over the NSAID-based era, then decreased significantly ($p = 0.001$) in the nonbiologic MTX period and in the nonbiologic and biologic era ($p < 0.01$).

“The composition of our cohort changed over time in a way that can [be] expected to increase disability over time,” including an increasing average age (57.2 years in 1983 vs 64.3 years in 2006) and disease duration (a mean of 14.4 years at cohort inception to 24.1 years in 2006). “Thus, the estimated declines in RA disability in the biological era are likely to be an underestimate of the true declines,” wrote the authors.

It was also postulated by the study authors that changing drug therapies as not the only contributor to the observed decrease in disability over time. For instance, smoking prevalence declined from 27.9% to just 5% among the study participants between 1992 and 2006.

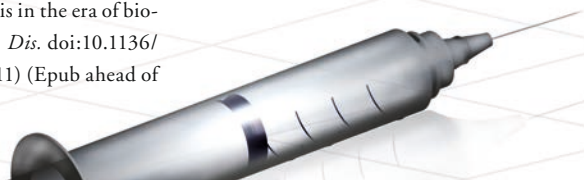
Speaking to the *International Journal of Clinical Rheumatology*, Krishnan concluded “Our study validates the expectation that the declines in disability in the pre-DMARD period has continued in the biologic era. Over time this can translate into better health outcomes such as mortality and morbidity, and perhaps may even result in cost savings to the society.”

– By Paolo Reveglia

Source: Krishnan E, Lingala B, Bruce B, Fries JF. Disability in rheumatoid arthritis in the era of biological treatments. *Ann. Rheum. Dis.* doi:10.1136/annrheumdis-2011-200354 (2011) (Epub ahead of print).

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Study suggests potential for omega-3-rich diets to prevent novel disease and reduce disease progression in osteoarthritis

Many reports in recent years have suggested a link between omega-3 levels in the body and the development or progression of rheumatological disease. However, scientific evidence is in short supply. Several recently completed studies, carried out in dogs, hint at the benefit of a high omega-3 diet for individuals with rheumatological disorders. Other research links diets low in omega-3 to the increase of inflammatory disease.

A study funded by Arthritis Research UK and published recently in *Osteoarthritis and Cartilage*, comes one step closer to confirming the link between a high omega-3 diet and reduced incidence of disease development in osteoarthritis (OA) in humans, following a dramatic 50% reduction of disease development seen in the study's animal models treated with a high omega-3 polyunsaturated fatty acid (PUFA) diet.

Researchers at the University of Bristol (Bristol, UK) examined the effect of PUFA diets on the progression of OA in a spontaneous guinea pig model. Dunkin-Hartley guinea pigs, prone to OA, were compared with OA-resistant Bristol strain-2 guinea pigs. Both were fed on a standard or a PUFA diet for 10–30 weeks.

OA-prone guinea pigs on the PUFA diet showed reduction in disease. Most of the measured cartilage parameters—active MMP-2, lysyl-pyridinoline and total collagen cross-links were modified by the PUFA diet to show patterns similar to those seen in the OA-resistant animals. Subchondrial bone parameters in the OA-prone animals given PUFA, also changed towards those seen in the nonpathological strain; significantly, calcium:phosphate ratios and epiphyseal bone density.

“...all of the evidence supports the use of omega-3 in human disease.”

Lead researcher, John Tarlton, from the Matrix Biology Research group at the University of Bristol's School of Veterinary Sciences, commented on the potential of the study's results to be transferable to humans, “The only way of being certain that the effects of omega-3 are as applicable to humans as demonstrated in guinea pigs is to apply omega-3 to humans. However, osteoarthritis in guinea pigs is perhaps the most appropriate model for spontaneous, naturally occurring osteoarthritis, and all of the evidence supports the use of omega-3 in human disease.”

Tarlton also commented on the potential for omega-3, not only to reduce novel OA development but also to potentially slow disease progression, “...there was strong evidence that omega-3 influences the biochemistry of the disease, and therefore not only helps prevent disease, but also slows its progression, potentially controlling established osteoarthritis.”

Results from this study highlight the importance of omega-3 as a potential contributing factor to the prevention of OA. Details from the study suggest not only does omega-3 prevent disease but has an effect on progression of disease. Omega-3 and its relationship to OA in humans remains unclear, however it is hoped that from these results and the results of similar trials that this relationship will not remain unclear for long.

— By Caroline Purslow

Sources: Knott L, Avery N, Hollander A, Tarlton J. Regulation of osteoarthritis by omega-3 (n-3) polyunsaturated fatty acids in a naturally occurring model of disease. *Osteoarthritis Cartilage* 19(9), 1150–1157 (2011); Fritsch DA, Allen TA, Dodd CE *et al.* A multicenter study of the effect of dietary supplementation with fish oil omega-3 fatty acids on carprofen dosage in dogs with osteoarthritis. *J. Am. Vet. Med. Assoc.* 236(5), 535–539 (2010).

AMISPRO[®] shows promise for treatment of scleroderma

Recently announced results of a Phase II trial have suggested Daval International's AMISPRO[®] to be safe and well tolerated as a monotherapy to patients with late-stage established diffuse cutaneous systemic sclerosis.

The double-blind, placebo-controlled study evaluated the effects of 4.5 mg/ml doses of AMISPRO twice weekly for 26 weeks compared with placebo. The primary end point of the study was to evaluate the safety and tolerability of AMISPRO in the treatment of 20 patients

with systemic sclerosis for a period of 26 weeks of study participation.

“In addition to these encouraging safety signs, AMISPRO showed signs of clinical benefit...”

At the end of this period, there were no signs of deterioration in hematological, cardiologic, biochemical or immunologic parameters measured. In addition to these encouraging safety signs, AMISPRO showed signs of clinical

benefit in secondary outcome measures including the modified Rodnan skin score, the Scleroderma UK Functional Score, the Patient and Physician Global Assessment (VAS), the SF-36 (short form 36) and the MRC Sum Score. The modified Rodnan skin score provides a validated measure of disease severity and in the study patients receiving placebo, a worsening was recorded (changes: -27.07%, $p = 0.29$) whereas a stability was observed in the AMISPRO-treated patients. Furthermore, there was a distinct

improvement in the overall SF-36 scores (changes: +41.6%, $p = 0.184$) for patients receiving AIMSPRO.

The results also demonstrated trends towards benefit for lung function measures. The forced expiratory volume in one second decreased in the placebo group as compared with baseline at 26 weeks (change: -5.6%; $p = 0.0582$). In contrast, no deterioration was observed in the AIMSPRO-treated group. Similarly, the forced vital capacity decreased in the placebo group as compared with baseline at 26 weeks (change: -5.6%, $p = 0.1038$),

but no change was observed in the AIMSPRO-treated group, where the forced vital capacity showed an increase (change: +1.8%; $p = 0.3225$).

“Although requiring further confirmatory studies, these results are quite exciting, especially when compared with what has been seen in other pilot trials in scleroderma as there is a clear unmet medical need for patients suffering with this life-threatening disease” enthused Christopher Denton, the principal investigator for the trial and Professor of Experimental Rheumatology at the Royal Free Hospital

in London, UK. “The important value of the safety data from such a well-conducted trial in such a serious disease is clear, apart from the signals of therapeutic benefit.”

Daval is now assessing the biomarker data collected in this clinical trial and correlating this with the changes observed, in order to shed more light into the mechanism of action of AIMSPRO in the context of late stage established diffuse cutaneous systemic sclerosis.

– By Paolo Reveglia

Source: Daval International. News and resources: www.davalinternational.com/news/news_3.html

Study results provide better understanding of rheumatoid arthritis disease mechanism

A new study, published in *PLoS ONE*, could potentially contribute to a more informed understanding of the mechanism of rheumatoid arthritis (RA) and could have an impact on the strategy taken for future clinical trials on the disease.

RA is a chronic and disabling autoimmune disease and the symptoms experienced, such as, inflammation, swelling around the joints affected and impaired motion can vary between individuals. According to Arthritis Research UK, RA is the second most common form of arthritis in the UK and the Arthritis Foundation states that RA is a disease affecting 1.3 million Americans.

Previous research demonstrated that there was high expression of the *CCR2* gene in the joints of RA patients and thus it was thought that *CCR2* could potentially play a role in the disease. Peng Liu (Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, NC, USA) explains, “Scientists thought that if you inhibited *CCR2* you would have a beneficial effect. But actually, the result was the

opposite.” It was in fact shown that inhibiting *CCR2* could not benefit joint inflammation and the disease even worsened in some instances.

“The study results could potentially lead to new directions for drug development, as Th17 inhibition could be a promising avenue.”

Since RA is an autoimmune disease, Liu and colleagues looked at “whether autoimmune-associated Th17 cells were involved in the pathogenesis of the severe phenotype of autoimmune arthritis.” Scientists discovered that in the draining lymph nodes of immunized *CCR2(-/-)* mice, there were three-times more Th17 cells than in wild type controls. Liu explains, “We found that an enhanced Th17 cell response is responsible, at least in part, for the increased disease severity.”

Results also showed that a certain type of monocyte was no longer present in the spleen, although they were abundant in

both the bone marrow and joints of the immunized *CCR2(-/-)* mice. Liu states, “The potential link between *CCR2* and the Th17 cells is the monocyte subset.” It could be that the monocyte expressing *CCR2* has a regulatory role, thus when the monocyte is not present, Th17 cells proliferate. Liu goes on to say, “Finding this monocyte may be important for later development of cell-based therapy.” The study results could potentially lead to new directions for drug development, as Th17 inhibition could be a promising avenue.

– By Roshaine Gunawardana

Sources: Rampersad RR, Tarrant TK, Vallanat CT *et al.* Enhanced Th17-cell responses render *CCR2*-deficient mice more susceptible for autoimmune arthritis. *PLoS ONE* 6(10), e25833 (2011); UNC Healthcare – News: <http://news.unchealthcare.org/news/2011/october/the-case-of-the-missing-monocyte>; Arthritis Research UK: www.arthritisresearchuk.org/arthritis_information/arthritis_types__symptoms/rheumatoid_arthritis.aspx; Arthritis Foundation: www.arthritis.org/types-what-is-rheumatoid-arthritis.php

in brief...

A motif in the V3 domain of the kinase PKC- α determines its localization in the immunological synapse and functions in T cells via association with CD28. Kong KF, Yokosuka T, Canonigo-Balancio AJ, Isakov N, Saito T, Altman A. *Nat. Immunol.* 12(11), 1105–1112 (2011). A new study has uncovered a previously unknown molecular interaction that is essential for T-lymphocyte activation and believed to potentially open the door to the development of new therapies for conditions like rheumatoid arthritis and other autoimmune-related diseases. The findings provide novel information regarding an enzyme known as protein kinase C- α and its interaction with CD28, a T-cell stimulatory factor long known to be involved in effective T-cell activation. The study investigators hope that targeting this interaction in T cells will be highly selective and consequently cause minimal undesirable side effects to other cells and tissues.

