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BSR: Multiple Benefits Seen With Intensive Psoriatic Arthritis Therapy

Sara Freeman

Multiple joint and skin benefits can be achieved by intensively treating patients with psoriatic arthritis (PsA) until they achieve a set of minimal disease activity (MDA) criteria (see Table), an expert said at the British Society for Rheumatology annual conference.

While data are mounting on the value of treating to target (otherwise known as *tight control*) in PsA, these stats lag significantly behind those for inducing and maintaining remission in rheumatoid arthritis (RA), noted Dr Philip Helliwell of the University of Leeds in England.

"There is half as much evidence in PsA as there is in rheumatoid arthritis," he observed. "But we've also got a heterogeneous disease, and what we are going to have to do moving forward is find out how to treat different phenotypic expressions of psoriatic disease," he said during a Special Interest Group on Spondyloarthropathies. "We're beginning to work toward that now."

Dr Helliwell is the principal investigator of the Tight Control of Psoriatic Arthritis (TICOPA) study, which he highlighted as an example of how targeting treatment to achieve MDA criteria (*Ann Rheum Dis*. 2010;69:48-53) could be beneficial, compared to standard care. A total of 206 patients with newly diagnosed PsA were enrolled in the study and then randomly assigned to receive either "tight control"—meaning an intensive management strategy—or standard care for 48 weeks.

Intensive treatment began with methotrexate at a dose of 15 mg/kg/wk, then rapid escalation to 25 mg/kg/wk at six weeks, if needed. If patients did not achieve five out of a set of seven MDA criteria for PsA, methotrexate was continued and sulfasalazine added, with dose escalation after four to eight weeks.

If MDA was still not achieved and patients did not meet criteria for biologics (according to NICE guidance), alternatives included swapping sulfasalazine for cyclosporine or leflunomide (again, with dose escalation as needed). Patients who did receive a biologic could switch to another anti-TNF agent if they did not respond after 12 weeks.

The primary endpoint data from the trial, reported previously, showed that a higher proportion of patients in the intensive management group achieved ACR20 at 48 weeks, compared with those in the standard care group (62% vs 45%, respectively; $P = .02$). A higher percentage of intensively managed patients also achieved ACR50 (51% vs 25%; $P = .0004$) and ACR70 (38% vs 17%, $P = .002$).

Skin symptoms, measured via the Psoriasis Area and Severity Index (PASI), showed significant improvement favoring intensive therapy over standard care. PASI20 was achieved by 72% of intensively managed patients and 52% of those who received standard care; PASI75, by 59% and 33%, respectively; and PASI90, by 40% and 20%, respectively.

The full results of the study, to be published in *The Lancet,* will include details on a variety of secondary outcomes, as well as the cost-effectiveness of the intensive management strategy versus the standard care approach. One of the key secondary outcomes of the trial was the effects of the two treatment strategies on other PsA symptoms (eg, enthesitis, dactylitis, and nail symptoms). No differences between the groups were observed, however, with similar decreases seen in the tight control and standard care groups.

There were no statistically significant differences in radiologic outcomes, which included baseline and end-of-treatment changes in the total modified Sharp van der Heijde (SVdH) score, the erosion score, and joint-space narrowing (JSN) score. While this might seem somewhat disappointing, "there wasn't a lot of radiologic progression going on anyway," Dr Helliwell pointed out. Overall, there was a difference of about 5% in the percentage of patients with at least one joint erosion at baseline and after 48 weeks of treatment.

The majority of radiographic change that did occur was JSN of the hands, Dr Helliwell said, adding that affected patients tended to be slightly older than those without JSN. However, this observation did not reach statistical significance.

"We've since looked for associations with ACPA [anticitrullinated protein antibodies]—about 7% of our patients were ACPA positive—but there is no relationship," he added. There was also no significant

association between levels of C-reactive protein and erosive disease.

There was a trend suggesting that patients with erosions may be more likely to have polyarticular disease than oligoarticular disease. A next step would be to look at radiologic progression in these two groups of patients in more detail.

More adverse events, including severe ones, were seen in the tight control arm, compared with the standard care arm. But not all of these were related to study treatment, and many were to be expected with methotrexate treatment, Dr Helliwell observed.

But is the intensive approach cost-effective when compared to standard care? Data suggest that it is. Although the incremental cost-effectiveness ratio (ICER) initially exceeded the £20,000–£30,000 (about $31,000-$47,000) threshold used by the UK National Institute for Health and Care Excellence to judge if a new treatment is cost effective, when certain factors were allowed for, the ICER was brought down to about £28,000 ($44,000), making it a cost-effective strategy.

PsA consists of five classical subtypes. The most common of these subtypes is polyarthritis (60% of patients), followed by oligoarthritis (30%). The remaining 10% of patients comprise those with arthritis mutilans, distal interphalangeal predominant disease, or spinal predominant disease. The clinical features of dactylitis and enthesitis are prevalent in about 40% and 50% of patients, respectively, and can occur in any subgroup.

TABLE
Minimal Disease Activity (MDA) Criteria for Psoriatic Arthritis

MDA is achieved when five of the following seven criteria are met.

- Tender joint count ≤ 1
- Swollen joint count ≤ 1
- Psoriasis Area and Severity Index score ≤ 1 or body surface area ≤ 3
- Patient pain visual analogue score (VAS) ≤ 15
- Patient global disease activity VAS ≤ 20
- Health assessment questionnaire ≤ 0.5
- Tender entheseal points ≤ 1

Source: *Ann Rheum Dis.* 2010;69:48-53.

Considering the heterogeneity of presentation, the challenge now will be to determine if all clinical subgroups of PsA could benefit from treatment to an MDA target with intensive management, or if some subgroups benefit more than others.

The TICOPA study was funded by Arthritis Research UK, with support from Pfizer. Dr Helliwell has received consulting fees from Pfizer.

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Subclinical Hyperthyroidism Linked to Higher Fracture Risk

Bianca Nogrady

Individuals with subclinical hyperthyroidism are at increased risk for hip and other fractures, according to the authors of a meta-analysis. The researchers examined data from 70,298 individuals—4,092 with subclinical hypothyroidism and 2,219 with subclinical hyperthyroidism—enrolled in 13 prospective cohort studies.

After adjusting for age, sex, and other risk factors, the researchers found that individuals with subclinical hyperthyroidism had a 28% increase in risk for any fracture and a 36% increased risk for hip fracture, compared to individuals with normal thyroid function.

Subclinical hyperthyroidism—defined as a thyroid-stimulating hormone (TSH) level < 0.45 mIU/L with normal FT4 levels—was also associated with a 16% increase in risk for nonspine fracture, according to a paper published online in *JAMA*. Men with subclinical hyperthyroidism had a more than 3.5-fold increase in risk for spine fracture, but the increased risk was not significant in women.

Lower TSH was associated with higher fracture rates. Analysis revealed a 61% increase in risk for hip fracture and a more than 3.5-fold increase in spine fracture risk among individuals with a TSH < 0.1 mIU/L.

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The analysis yielded no link between subclinical hypothyroidism and fracture risk. A comparison of fracture risk between individuals treated with thyroxine at baseline and untreated participants showed no impact of therapy on fracture outcomes (*JAMA*. 2015 May 26 [doi:10.1001/jama.2015.5161]).

"In prospective cohort studies, data about the association between subclinical thyroid dysfunction and fracture risk are in conflict because of inclusion of participants with overt thyroid disease and small [samples] of participants with thyroid dysfunction or fracture events," wrote Dr Manuel R. Blum, of Bern University Hospital, Switzerland, and an international team of co-authors.

They proposed three mechanisms by which thyroid dysfunction may affect fracture risk.

"First, thyroid hormones have been shown to have effects on osteoclasts and osteoblasts, with thyroid status in the upper normal range or excess thyroid hormones leading to accelerated bone turnover with bone loss and increased fracture risk," they wrote.

Subclinical hyperthyroidism may also increase the risk for falls by affecting muscle strength and coordination. It was also suggested that thyroxine supplementation might have an impact on fracture risk.

"Endogenous subclinical hyperthyroidism may be undetected for years because symptoms of subclinical hyperthyroidism are often nonspecific or absent," the authors wrote. "This phenomenon has the potential to lead to a greater length of time for adverse associations with bone metabolism."

The authors stressed the limitations of the observational data (for example, thyroid function was assessed only at baseline, and some individuals may have progressed to overt thyroid dysfunction over the course of the study) and the lack of a uniform definition of fracture type across the cohorts.

They said their findings support current guideline recommendations that persons ages 65 or older with subclinical hyperthyroidism and a TSH persistently < 0.1 mIU/L should be treated, and treatment should be considered in individuals with a low TSH that is still above 0.1 mIU/L.

The Swiss National Science Foundation and Swiss Heart Foundation supported the study. Some authors disclosed personal fees, grants, and funding from a range of pharmaceutical companies.

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Newer Oral Contraceptives Pose Higher VTE Risk

Tara Haelle

The risk for venous thromboembolism (VTE) is generally greater for women using oral contraceptives with newer types of progestogen hormones than for those taking older, second-generation birth control pills, study results showed.

"Women exposed to drospirenone, gestodene, cyproterone, and desogestrel within the last 28 days had around a four times increased risk for venous thromboembolism," the investigators found. Women exposed to levonorgestrel, norethisterone, and norgestimate had about a 2.5 times greater risk for VTE than did women not exposed in the past year, said Yana Vinogradova and her colleagues at the University of Nottingham in England (*BMJ*. 2015 May 26 [doi:10.1136/bmj.h2135]).

The researchers conducted two nested case-control studies using data from 618 primary care practices in the Clinical Practice Research Datalink (CPRD) and 722 practices in the QResearch primary care database. A total of 5,062 cases from CPRD and 5,500 cases from QResearch were matched 1:5 with 19,638 and 22,396 controls, respectively.

Approximately 29% of CPRD patients and 26% of QResearch patients used oral contraceptives, most commonly levonorgestrel. Overall, any use of combined oral contraceptives resulted in a three times increased risk for VTE, compared with no use in the past year.

After accounting for smoking, obesity, a wide range of other health conditions, alcohol con-

sumption, polycystic ovary syndrome and recent infections, surgeries, leg/hip fractures, and hospital admission, the researchers found an increased likelihood of VTE associated with each hormone: desogestrel (odds ratio [OR], 4.28), cyproterone (OR, 4.27), drospirenone (OR, 4.12), gestodene (OR, 3.64), levonorgestrel (OR, 2.38), norgestimate (OR, 2.53), and norethisterone (OR, 2.56). The increased VTE risk in patients on these hormones was compared with no exposure to oral contraceptives in the previous year.

In terms of numbers needed to harm, the researchers estimated that use of levonorgestrel and norgestimate resulted in six extra cases of VTE each year per 10,000 treated women ages 15 to 49, and seven extra cases for women ages 25 to 49.

Desogestrel and cyproterone each contributed 14 additional cases of VTE each year per 10,000 treated women ages 15 to 49, and drospirenone, desogestrel, and cyproterone each contributed to an extra 17 cases of VTE each year per 10,000 women ages 25 to 49.

"We believe this study has the statistical power and sufficient adjustment for relevant confounders to be regarded as an important clarifying study, which has produced the most reliable possible risk estimates using currently available UK prescription data," the researchers wrote.

There was no external funding for the study. Julia Hippisley-Cox is the unpaid director of QResearch, a not-for-profit organization that is a joint partnership between the University of Nottingham and EMIS, a commercial IT supplier. She is also a paid director of ClinRisk, which produces clinical risk algorithm-related software.

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Statins, Fibrates Lower Stroke Risk in Elderly

Mary Ann Moon

Both statin and fibrate therapies taken to improve lipid profiles decreased risk for stroke by 30% in a community-dwelling population of elderly people, according to a prospective European study published online in the *British Medical Journal*.

Participants in almost all the randomized clinical trials assessing cardiovascular (CV) drugs are younger than 70, so the benefits of these agents in older patients—particularly their effectiveness as primary prevention in those who have no known CV illness—are uncertain. Nevertheless, "in real life, statins are commonly prescribed to older people without clinical evidence of atherosclerosis," said Dr Annick Alperovitch of the University of Bordeaux (France) and her associates.

To assess the effects of statin and fibrate therapies on incident CV events in an elderly population, the investigators analyzed data from an ongoing cohort study of vascular disease among elderly residents of Bordeaux, Dijon, and Montpellier. Dr Alperovitch and her associates examined the medical records of a subset of 7,484 men and women (mean age, 74) who were followed every two years for a mean of nine years. A total of 27% reported using lipid-lowering medications at baseline; roughly half used statins and half used fibrates. There were 292 strokes during follow-up.

The risk for stroke was cut by roughly 30% among statin and fibrate users, compared with nonusers (hazard ratio [HR], 0.66). This decrease was similar between the two medications. All-cause mortality was slightly lower in people who took statins or fibrates, compared with nonusers (HR, 0.87), the investigators said (*BMJ*. 2015 May 19 [doi:10.1136/bmj.h2335]).

This is the first observational study to show a significant association between lipid-lowering drugs and decreased stroke risk, they noted.

The overall incidence of stroke in this study was low (0.47 per 100 person-years), so even a 30% decrease produced "a limited number of avoided cases." That may be attributable in part to the generally healthy lifestyle, high educational achievement, and high economic status of this urban French study

population. But if the findings are confirmed in future studies, they could have an important impact on public health in other populations, Dr Alperovitch and her associates said.

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Cystic Fibrosis–related Diabetes Requires Different Approach

Bruce Jancin

Cystic fibrosis–related diabetes (CFRD) is a unique disease that requires a different mindset on the part of the treating clinician.

"The risk for cardiovascular death drives a lot of the recommendations for management of our patients with type 1 and type 2 diabetes, but this doesn't apply in cystic fibrosis [CF]," Dr Antoinette Moran asserted at the annual meeting of the Pediatric Academic Societies. "Patients with CFRD do not appear to get macrovascular complications. These patients have other, more important concerns—namely, survival. They die from their CF lung disease. Diabetes is important, but we have to remember that in CF, lung function and nutrition come first. It's our job to work around that."

Diabetes is the most common comorbidity associated with CF, and it spells big trouble. It's associated with pancreatic insufficiency, liver dysfunction, need for corticosteroids, and (prognostically) undernutrition, worse pulmonary function, and early death, noted Dr Moran, Professor of Pediatrics and Chief of the Division of Pediatric Endocrinology and Diabetes at the University of Minnesota, Minneapolis.

The prevalence of CFRD varies by age. It's rare in children, but the prevalence climbs to about 15% in adolescents, 40% in persons ages 20 to 39, and 55% in those 40 and older.

"In fact, more than 80% of CF patients with the most severe mutations have diabetes by the time they're 40," according to Dr Moran, who was lead author of CFRD management guidelines released last year by the International Society for Pediatric and Adolescent Diabetes (*Pediatr Diabetes*. 2014;15 (suppl 20):65-76).

CFRD is not an autoimmune disease. Ketones are rare, and glycosylated hemoglobin levels are spuriously low. The definitive treatment is insulin.

"Remember, you're not just treating hyperglycemia, you're treating insulin deficiency. Insulin deficiency is really the hallmark of this disease. It is progressive and eventually severe, but not complete—unlike in type 1 diabetes," she observed. "Treatment of patients in their well state is similar to treating type 1 diabetes in the honeymoon phase. However, during acute illness, patients become extremely insulin resistant. It's a black hole that you can pour insulin into, and sometimes you can't get them to budge. Then a couple of months later, they're insulin sensitive again."

Multiple studies have demonstrated that diabetes has a negative impact on survival in patients with CF. Both hyperglycemia and insulin insufficiency have negative impacts on CF lung disease.

Insulin is a potent anabolic hormone that's necessary for maintenance of body weight and lean body mass, and insulin insufficiency leads to a catabolic state that accelerates pulmonary decline in CF. Studies show that nutritional status and pulmonary function start to decline in CF patients several years before they're diagnosed with diabetes. Thus, by the time CFRD is diagnosed, patients have already experienced several years of insulin insufficiency, with adverse consequences.

Moreover, when blood glucose levels exceed 144 mg/dL, glucose appears in the airways of CF patients, which probably promotes pulmonary infection. Anecdotal evidence suggests hyperglycemia makes sputum thicker and more difficult to clear, as well as boosting bacterial growth. And continuous glucose monitoring studies conducted in patients with CFRD indicate they spend roughly half of each day with a blood glucose level in excess of 144 mg/dL.

Aggressive screening and early initiation of insulin therapy help reverse chronic weight loss and reduce mortality in patients with CFRD. The various

guidelines recommend annual screening for diabetes in CF patients starting by age 10.

"I personally believe it should begin much earlier than that," Dr Moran said, citing a study led by her Minnesota colleague, Dr Katie L. Ode, that showed that abnormal glucose tolerance was already present in 41% of children with CF at ages 6 to 9, and that those children had a high rate of early-onset CFRD (*Pediatr Diabetes*. 2010;11:487-492).

The oral glucose tolerance test, performed when the patient is clinically stable, is the screening tool of choice for CFRD.

"It's not that it's such a great test—we all know it has problems—but the other tests perform poorly in CF. And a diagnosis based on an oral glucose tolerance test correlates with prognosis and future outcomes, so you get meaningful data when you do it," Dr Moran explained.

Evidence-based guidelines for CFRD put forth jointly by the American Diabetes Association, Cystic Fibrosis Foundation, and Lawson Wilkins Pediatric Endocrinology Society (*Diabetes Care*. 2010;33:2697-2708) emphasize that the diagnosis of CFRD can be made while a patient is hospitalized with an acute illness. The criterion is fasting or postprandial hyperglycemia persisting for more than 48 h after hospitalization.

"Why are we calling this diabetes? These patients have repeated bouts of acute illness. The CF patient you're seeing today in the hospital may very well be back in five months, and again two months after that. It's a frequent event in these patients, and when their diabetes persists for longer than 48 hours, it tends to persist for weeks before their need for insulin goes away—until the next time they get sick," Dr Moran said. "But most of these patients spend a substantial amount of time each year hyperglycemic. And most importantly, if you use as your date of diagnosis diabetes that's present at the time of an acute illness, it correlates with microvascular complications and with mortality. So it establishes a meaningful start point for future risk."

Dr Moran reported financial relationships with Novo Nordisk and Vertex.

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CVD Risk Persists for 40 Years in Hodgkin Survivors

Mary Ann Moon

People who survive Hodgkin lymphoma in adolescence or young adulthood remain at very high risk for cardiovascular disease (CVD) for at least 40 years—the longest period for which they have been followed, according to the results of a retrospective cohort study of more than 2,500 patients.

Until now, follow-up studies of such patients "rarely exceeded 20 to 25 years," before most survivors reached the age at which CVD becomes commonplace in the general population. To compare CVD rates between survivors and the general population at later ages, investigators examined the medical records of 2,524 individuals who survived five years or more after treatment for Hodgkin lymphoma as adolescents or young adults at five Dutch medical centers between 1965 and 1995.

A total of 81% of the cohort had received mediastinal radiotherapy and 31% had received anthracycline-containing chemotherapy. After five to 47 years of follow-up, 797 of these patients experienced 1,713 cardiovascular events. The most frequently occurring events included 401 coronary heart disease (CHD) events (such as MI and angina pectoris), 374 valvular heart disease events, and 140 heart failure (HF) events (such as cardiomyopathy and congestive heart failure), Frederika A. van Nimwegen, of the Department of Epidemiology at the Netherlands Cancer Institute in Amsterdam, and her colleagues wrote in *JAMA Internal Medicine* (doi:10.1001/jamainternmed.2015.1180).

Compared with the general population, Hodgkin survivors had a 3.2-fold higher standardized incidence ratio (SIR) for CHD and a 6.8-fold higher SIR for HF, corresponding to 70 excess cases of CHD and 58 excess cases of HF per 10,000 person-years.

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These risks were significantly higher for survivors than for the general population at all ages, but patients who had been diagnosed and treated before the age of 25 were at particularly elevated risk: they carried a 4.6- to 7.5-fold higher risk for CHD and a 10.9- to 40.5-fold higher risk for HF. At 40 years after Hodgkin diagnosis and treatment, the cumulative incidence of any type of CVD was 50%, the investigators wrote. Both survivors of Hodgkin lymphoma and their clinicians should be aware that these patients remain at substantially increased cardiovascular risk throughout their lives, Ms van Nimwegen and her colleagues wrote.

This study was supported by the Dutch Cancer Society. Ms van Nimwegen and her colleagues reported having no financial disclosures.

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Asymptomatic Carotid Stenosis and Central Sleep Apnea Linked

Bianca Nogrady

More than two-thirds of patients with asymptomatic carotid stenosis are likely to have sleep apnea, according to an observational study. The polysomnography results of 96 patients with asymptomatic extracranial carotid stenosis revealed that 69% had sleep apnea: 42% had obstructive sleep apnea (OSA) and 27%, central sleep apnea (CSA).

Stenosis severity was significantly associated with CSA but not OSA. Researchers found that CSA, but not OSA, was associated with arterial hypertension and diabetes in those patients with asymptomatic carotid stenosis (*CHEST*. 2015;147:1029-1036 [doi:10.1378/chest.14-1655]).

Patients ranged in age from 39 to 86 (mean age, 70). Of the 96 patients, 64 were men; 21 had mild/moderate stenosis and 75 had severe carotid stenosis. Patients with severe stenosis were older (average age, 67) than those with mild/moderate stenosis (average age, 61). The frequency of arterial hypertension and diabetes was higher in the severe stenosis group than in the mild/moderate stenosis group.

The prevalence of sleep apnea was 76% in patients with severe stenosis, compared with 29% in those with mild/moderate carotid stenosis. Total apnea-hypopnea index was higher in the severe stenosis group compared with the mild/moderate stenosis group ($P \leq .009$). Increase in sleep apnea severity was based on an increase in central apnea-hypopnea index ($P \leq .001$) but not in obstructive apnea-hypopnea index, reflecting an augmentation of CSA and not of OSA in patients with severe compared with mild/moderate carotid stenosis.

"This vascular risk constellation seems to be more strongly connected with CSA than with OSA, possibly attributable to carotid chemoreceptor dysfunction," wrote Dr Jens Ehrhardt and colleagues at Jena University Hospital, Germany.

No conflicts of interest were declared.

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