



An Overview and Update on Ankylosing Spondylitis (Marie-Strumpell Disease)

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Objectives:

1. Recognize and distinguish symptoms of ankylosing spondylitis.
2. Discuss the prevalence and pathogenesis of ankylosing spondylitis.
3. Interpret useful information from clinical studies using new biologic agents to treat ankylosing spondylitis.
4. Describe a general overview of the current treatment of ankylosing spondylitis.

Ankylosing spondylitis (AS) is a member of a group of disorders categorized as spondyloarthropathies, or diseases of the joints of the spine.¹ Other spondyloarthropathies include Reiter's syndrome, reactive arthritis, psoriatic arthritis and spondylitis, enteropathic arthritis and spondylitis, and juvenile-onset and undifferentiated spondyloarthropathy. All of these disorders share some similar clinical features and an association to the human leukocyte antigen, HLA-B27 allele.

About the Author:



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Ankylosing spondylitis is the prototypical spondyloarthropathy. "Ankylosing spondylitis is a chronic inflammatory disease of the joints of the axial skeleton, manifested clinically by pain and progressive stiffening of the spine."² Peripheral joints and extraarticular structures may also be affected. Acute anterior uveitis is one of the more common extraarticular manifestations of AS.³

The prevalence of AS is considered to be about 0.1-0.2% of the population, but could be as high as 1.4%.^{4,5} In comparison, the prevalence of rheumatoid arthritis is estimated at 1%.⁶ The pathogenesis is not known, but a combination of genetic, immunological, and infectious environmental factors are thought to be involved.³

Ninety percent of the patients with AS have the HLA-B27 allele in their genetic profile.² New research has identified 23 subtypes of HLA-B27 (B*2701 to B*2723).³ AS has been positively associated with the first 10 subtypes except for subtypes B*2706 and B*2709 that show limited or no relation to AS. Based

on a sample of blood donors, the prevalence of AS in the population of Berlin, Germany was estimated to be 0.86% with an estimated 9.3% of the population having the HLA-B27 frequency.⁷ Presence of HLA-B27 alone is not indicative of AS but is considered a risk factor. Other risk factors for AS include family history of AS, male gender, and frequent gastrointestinal (GI) infections.³

Men develop AS 2 to 3 times more frequently than women.⁸ Typically, AS begins in the second or third decade of life but it is not uncommon for there to be a long delay from the time of the initial presentation to the time a definitive diagnosis of AS is made.⁹ In a survey of 1080 AS patients, the average age of disease onset was 24.8 years in HLA-B27 (+) patients and 27.7 years in HLA-B27 (-) patients.⁹ The average age at diagnosis was 33.2 years in HLA-B27 (+) patients and 39.1 years in HLA-B27 (-) patients. Sacroiliitis, or inflammation of the joint between the sacrum and ilium, is often the initial manifestation of the

IN THIS ISSUE

5 CE ASSESSMENT QUESTIONS

6 GHANAIAN VISITING SCHOLAR PHILIP ANUM RECEIVES CUSTOMIZED TRAINING AT DDIS

7 NEW FDA APPROVALS

8 KEY REFERENCES FOR NEW DRUGS

9 PERSPECTIVE FROM AN *IDIS* SUBSCRIBER: COGNITIVE DYSFUNCTION/ SEVERE PSYCHIATRIC DISORDERS POSSIBLY ASSOCIATED WITH NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND COX-2 INHIBITORS IN THE ELDERLY—MORE COMMON THAN WE HAVE BEEN LED TO BELIEVE?

disease.¹ Patients present complaining of chronic lower back pain, felt deep in the buttocks and/or in the lower lumbar regions.³ The pain is often worse at night or after periods of inactivity. Persons with AS experience loss of spinal mobility, restriction of flexion and extension of the lumbar spine, and decreased chest expansion. The course of the disease is unpredictable and varies from person to person in manifestation and severity. The less severe the disease progression during the first 10 years, the less likely it will progress to severe disease. There is no cure for AS so conventional treatment is aimed at treating the aches, pains, and inflammation of this chronic progressive disease.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of AS. NSAIDs provide improvement in inflammatory back pain and are considered the cornerstone of treatment.¹⁰ Patients often experience a rapid and significant decrease in pain upon starting NSAID therapy. There is no agreement, however, as to whether AS patients should take NSAID therapy continuously or only during disease flare-up. The argument against continual NSAID treatment is based on the potential for GI adverse effects.¹⁰ Generally, however, pain quickly returns for many patients who discontinue NSAID treatment.

Some patients become refractory to NSAIDs, or side effects limit their use. Disease modifying antirheumatic drugs (DMARDs) such as sulfasalazine, azathioprine, anti-malarials, methotrexate, and gold salts are second-line agents for AS. The effectiveness of these agents in treating AS has been variable and unremarkable.^{10,11} Corticosteroids may be used, but rheumatologists believe systemic corticosteroids are less effective for treating the

spondyloarthropathies than for treating rheumatoid arthritis. In AS patients, intraarticular corticosteroid therapy has been more successful than systemic therapy.³ Pamidronate has shown some efficacy in treating AS patients. In a recent study, 63% of patients receiving pamidronate 60 mg intravenously had at least a 25% improvement after 6 months of therapy.¹²

Two relatively new biologic drugs, the anti-tumor necrosis factor-alpha (anti-TNF- α) agents infliximab and etanercept, recently have shown great promise in treating patients with AS. Etanercept is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton tumor necrosis factor receptor linked to the Fc portion of human IgG1.¹³ Similarly, infliximab is a chimeric IgG1 κ monoclonal antibody.¹⁴ Both of these biologics act by specifically binding to tissue necrosis factor and thus blocking its interaction with cell surface TNF receptors. Patients with AS have significantly higher serum levels of TNF compared to patients with non-inflammatory back pain.¹⁵ High amounts of TNF- α messenger RNA and protein have also been found in the sacroiliac joint biopsies of AS patients.

Infliximab (Remicade[®]) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of Crohn's disease in 1998 and has since been approved for treatment of rheumatoid arthritis in combination with methotrexate.^{14,16} Infliximab also has shown promising results in 3 randomized trials treating psoriasis.¹⁷⁻¹⁹

Three randomized controlled studies have evaluated the efficacy of infliximab in patients with

AS. In a study by Braun et al,²⁰ 70 patients with severe AS were randomized to treatment with once weekly 2-hour intravenous infusions of infliximab 5 mg/kg or placebo at weeks 0, 2, and 6. The primary efficacy endpoint was improvement of disease activity by 50% at the end of 12 weeks compared to baseline as measured by the Bath ankylosing spondylitis disease activity index (BASDAI). Through a questionnaire, the BASDAI measures disease activity both qualitatively and quantitatively based on fatigue, spinal pain, peripheral arthritis, enthesitis, and morning pain. DMARDs and corticosteroids were stopped at least 4 weeks before screening. Patients were allowed to continue using NSAIDs, but the dose could not be increased over the baseline value. At week 12, 53% of infliximab patients showed a 50% improvement in the BASDAI compared to 9% of placebo patients. NSAID therapy was reduced by more than 50% of baseline value in 18 of 34 infliximab patients and stopped completely in 13 infliximab patients. Fifty-one percent of placebo patients (18/35) and 35% (12/34) of infliximab patients developed upper respiratory infections. Three infliximab patients had to be withdrawn from the study; one with systemic tuberculosis, one with allergic granulomatosis of the lung, and the third with transient leukopenia.

In an open, observational extension of this study, 65 of the 70 infliximab and placebo treated patients went on to receive infliximab 5 mg/kg every 6 weeks for a total of 54 weeks.²¹ At week 54 in the intent-to-treat analysis, 47% of the patients in the infliximab/infliximab group and 51% of the patients in the placebo/infliximab group scored a 50% improvement in the BASDAI score. By the end of the study, nearly 70% of the patients had

reduced their NSAID dose. No further cases of tuberculosis, granulomatosis of the lung or leukopenia appeared during the extension study. Seventeen of 69 patients (25%), however, developed detectable levels of antinuclear antibodies (ANAs). At baseline, 1 patient in the infliximab group and no patient in the placebo group were ANA positive. Of the 17 ANA positive patients, 3 showed possible ANA-associated musculoskeletal symptoms. In 2 of these patients, the symptoms resolved upon discontinuation of infliximab and treatment with methylprednisolone. The third patient developed chronic polyarthritis.

In another study by Van den Bosch et al,²² 40 patients with active spondyloarthropathies, defined as the presence of at least 1 swollen joint or 1 current episode of active tendinitis or dactylitis and/or inflammatory spinal pain, were randomly assigned to treatment with once weekly intravenous infliximab 5 mg/kg or placebo at weeks 0, 2, and 6. Ten of the 40 patients had AS. The patients were followed for 12 weeks. DMARDs were not allowed during the study and had to have been discontinued at least 4 weeks prior to the study. NSAIDs and corticosteroids were allowed to continue during the study. Patient and physician assessments of global disease activity measured on a 100-mm visual analog scale at week 12 were the primary efficacy endpoints. At baseline, the average patient global assessment of disease activity was 53.5 (placebo) versus 67 (infliximab), and at week 12, it was 69 (placebo) versus 18 (infliximab). At baseline, the average physician global assessment of disease activity was 66.5 (placebo) versus 67.5 (infliximab) and at week 12,

it was 72 (placebo) versus 16.5 (infliximab). By both patient and physician assessment, infliximab therapy was superior compared to placebo ($p < 0.001$). One patient receiving infliximab developed systemic tuberculosis and was removed from the study. Another patient receiving infliximab was removed from the study because of septic arthritis though it was not believed to be related to infliximab therapy. All other reported side effects were minor.

In a third study, to evaluate a magnetic resonance imaging (MRI) scoring system to assess spinal inflammation in AS patients, 20 patients with active, severe AS (BASDAI > 4) were examined.²³ Nine of the 20 patients were randomized to receive weekly infusions of infliximab 5 mg/kg at weeks 0, 2, and 6 and the balance to placebo. At the end of three months, a worsening of all clinical parameters was seen in the placebo group. The average BASDAI at baseline was 5.88 for the placebo group and 5.89 at the end of three months. Conversely, in the infliximab group, the BASDAI changed from 6.35 at baseline to 3.35 at the end of 3 months. With a clinical response defined as a greater than 50% improvement in the BASDAI, there were only 2 responders in the placebo group (18%) versus 5 responders in the infliximab group (56%) ($p < 0.05$). In addition to the clinical success, significant regression of spinal inflammation also was shown using the MRI activity scores.

Etanercept (Enbrel[®]) was originally approved by the FDA for the treatment of rheumatoid arthritis.²⁴ On July 24, 2003, Enbrel[®] was

approved for the treatment of AS.²⁵ This approval was based on a single randomized, controlled study of 277 patients. Fifty-eight percent of the patients receiving etanercept twice weekly for six months reported significant improvement in pain, function, and inflammation compared to 23% of the placebo patients. Side effects were similar to those seen in previous studies.

There have been other studies examining the use of etanercept in patients with AS. In a study by Gorman et al,²⁶ forty patients with active AS were randomized to treatment with subcutaneous etanercept 25 mg twice weekly for four months. Active AS was defined as the presence of inflammatory back pain, morning stiffness for at least 45 minutes, and at least moderate disease activity as assessed by the patient and physician. Patients were allowed to continue concomitant therapy with NSAIDs, oral corticosteroids, gold injections, methotrexate, and sulfasalazine as long as the dose had not been changed at least four weeks before randomization and was not increased during the study. Treatment response, the primary efficacy endpoint, was defined as at least a 20% improvement in at least 3 of 5 measures of disease activity: duration of morning stiffness, degree of nocturnal spinal pain, BASDAI, patients' global assessment of disease activity, and the score for joint swelling. Eighty percent of the etanercept patients in the intent-to-treat population experienced at least a 20% improvement compared to only 30% of the placebo-treated patients. The most common adverse events were reactions at injection site and minor infections. Upper respiratory infections occurred in 10 etanercept-

treated patients and 12 placebo-treated patients.

Unlike the previously mentioned study,²⁶ another recent study²⁷ was designed to show the efficacy of etanercept in treating AS in patients who had discontinued or were not taking DMARDs or corticosteroids. Forty patients with active AS (BASDAI of > 4) and a spinal pain score of > 4 on a 0-10 numeric scale were randomized to treatment with twice weekly subcutaneous etanercept 25 mg or placebo for six weeks. After six weeks, both groups received etanercept. All patients received etanercept for a total of 12 weeks. Follow-up continued until the end of six months. Concomitant NSAID therapy was allowed with no increase in dose over baseline dosage. The primary efficacy endpoint was defined as an improvement of disease activity of $> 50\%$ between baseline and week 6, measured by the BASDAI. By week 6 in the intent-to-treat population, 57% (8/14) of etanercept-treated patients had achieved a $> 50\%$ improvement in the BASDAI versus 6% (1/16) of placebo-treated patients. Seventy-one percent of the patients who received etanercept for 12 weeks showed a 50% response. Fifty-six percent of the patients who received etanercept for six weeks after placebo treatment had a 50% response. Pain at the injection site and minor infections were the most common adverse events. Six patients in both the placebo and etanercept groups had minor uncomplicated upper respiratory infections.

Infliximab and etanercept may be the most significant advancement since NSAIDs in the treatment of AS. Efficacy of

these agents has been shown, but they are still relatively new and the full-range and severity of toxicities may not yet be known. The studies so far have been short term. Results of long-term therapy in AS are not known. The results of early research with anti-TNF- α agents have identified 7 types of adverse events that are to be closely watched in further studies: infections, including sepsis and tuberculosis; malignancies, such as lymphoma; hematological disorders; demyelinating disorders and neuropathies; exacerbation of congestive heart failure; production of autoantibodies and autoimmune response; and infusion or injection and hypersensitivity reactions.¹⁵ A consensus statement on the use of biological agents in rheumatic diseases advises that the individual differences in disease aggressiveness, concomitant structural damage, the effect of the disease on a patient's quality of life, and the signs and symptoms of the disease should all be considered prior to initiating therapy with biological agents.²⁸ Toxicity of previous DMARD therapy should also be taken into account. The statement warns that TNF blocking agents should not be started or should be discontinued when serious infections occur and that previous tuberculosis may be reactivated. Demyelinating-like disorders have also been reported in patients using TNF blocking drugs, and patients with a definite history of demyelinating disease should not receive such agents.

Pharmacotherapy is an integral part in treating patients with AS, but routine exercise needs to be incorporated into AS treatment plans. Drug therapy alone is not enough to prevent stiffness and spinal

deformity. Exercise and physical therapy in combination with drug therapy are considered to be essential to achieving the best treatment outcome for patients with AS.¹⁰ A Cochrane review on physiotherapy exercise in AS found that physiotherapeutic exercises performed in supervised groups have some short term beneficial effects compared to home exercise programs.²⁹ The review concluded that more research in this area was needed to be able to recommend a specific physiotherapy exercise program for a patient with AS.

Conclusion

Ankylosing spondylitis, like other chronic diseases, requires long-term therapy that may change over the course of the disease. The mainstay of treatment of AS is the relief of symptoms using NSAIDs and physical therapy. As the disease progresses, therapy needs to expand to prevent further deterioration. The success of the anti-TNF- α agents has provided insight into the treatment of severe AS and may eventually lead to other treatments in this area. Given the positive treatment outcomes of both infliximab and etanercept in AS patients, comparative studies between these two drugs may be the next logical step in determining where these two agents fit into the overall treatment of AS. As the research in AS progresses, hopefully so too will the quality of life and overall well being of AS patients.

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(continued on page 12)



Accreditation Information

The University of Iowa College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. The ACPE program number is 020-000-03-024-H01. The University of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.

To earn continuing education credit, complete the assessment exercise, CE registration form and program evaluation on page 5, and return to Division of Drug Information Service with a \$5.00 check for the processing fee, made out to the College of Pharmacy. A certificate will be awarded upon achieving a passing grade of 70% or better. Pharmacists must complete this program by October 1, 2004 to receive credit.

CE REGISTRATION

TITLE OF EDUCATIONAL ACTIVITY (ARTICLE)
ACPE # 020-000-03-024-H01

An Overview and Update on Ankylosing Spondylitis (Marie-Strumpell Disease)

NAME _____

ADDRESS _____

CITY _____ STATE _____ ZIP _____

SOCIAL SECURITY NUMBER (OPTIONAL) _____

PHARMACY LICENSE NUMBER(S) _____

I HEREBY CERTIFY THAT I HAVE TAKEN THIS TEST:

Signature/Date _____

(circle the correct answer)

1. Which of the following drugs would not be considered a first or second line agent in treating ankylosing spondylitis?
 - a. indomethacin
 - b. codeine
 - c. methotrexate
 - d. sulfasalazine
2. TNF- α blocking agents are contraindicated in persons who:
 - a. are HLA-B27 (-).
 - b. are HLA-B27 (+).
 - c. are currently taking corticosteroids.
 - d. have a history of demyelinating disease.
3. Which of the following statements is true?
 - a. Presence of the HLA-B27 allele is a risk factor for AS.
 - b. To be diagnosed with AS, a person must be positive for the HLA-B27 allele.
 - c. Persons with AS should avoid stretching and exercising to prevent further back irritation.
 - d. Women develop AS more frequently than men.
4. Which of the following statements is true?
 - a. Tuberculosis has developed in some patients taking TNF- α blocking agents.
 - b. DMARDs are first line agents in treating AS.
 - c. Typically, patients with AS initially present with a stiff neck.
 - d. AS is quickly and easily diagnosed in most patients.
5. Which of the following statements is true?
 - a. Enbrel[®] is not FDA approved for treatment of AS.
 - b. DMARDs are highly effective in treating AS.
 - c. The pathogenesis of AS may in part be linked to infection.
 - d. Etanercept is a cure for AS.
6. Ankylosing spondylitis is:
 - a. a chronic progressive disease.
 - b. a chronic infection of the sacroiliac joint.
 - c. frequently associated with the HLA-B2706 allele.
 - d. seen primarily in geriatric patients.

7. All of the following side effects of anti-TNF- α therapy are of concern EXCEPT:
 - a. lymphoma
 - b. demyelinating disorders
 - c. tuberculosis
 - d. nausea and vomiting
8. Which of the following is a common extraarticular manifestation of AS?
 - a. psoriasis
 - b. demyelinating disease
 - c. gastrointestinal infection
 - d. anterior uveitis
9. All of the following are risk factors for AS EXCEPT:
 - a. sibling with AS
 - b. male
 - c. gastrointestinal infection
 - d. anterior uveitis
10. The prevalence of AS is estimated to be:
 - a. 0.1-0.2%
 - b. 0.001-0.002%
 - c. 2.1%
 - d. 9.3%

PROGRAM EVALUATION

	Excellent				Poor	
Overall quality	5	4	3	2	1	
Relevance to practice	5	4	3	2	1	
Value of content	5	4	3	2	1	
Important to pharmacists	Agree				Disagree	
	5	4	3	2	1	
Increased my knowledge	5	4	3	2	1	
Achieved stated objectives	5	4	3	2	1	
Was educational and not promotional	5	4	3	2	1	

It took me _____ hours and _____ minutes to read this article and complete the assessment questions.

Ghanaian Visiting Scholar Philip Anum Receives Customized Training at DDIS



Philip Anum, MSc., Coordinator-NDIS and Head-NDIRC

Philip Anum, a Visiting Scholar from Accra, Ghana, spent four weeks in July in the Division of Drug Information Service (DDIS) receiving customized instruction in drug information and informatics.

Anum is the coordinator for the National Drug Information System (NDIS) in Ghana, a program implemented within the Ministry of Health to ensure that objective information concerning effective and safe use of medications is available and easily accessible. He is also the head of Ghana's National Drug Information Resource Center (NDIRC).

As Anum explained, the NDIRC is "a mother who has been created to give birth to the other components of the NDIS." The other components will include a hierarchical network of peripheral drug information units in teaching hospitals, regional hospitals, district hospitals, and local facilities. Of course, as Anum pointed out, it would be impossible to replicate at each level all resources, such as computers and reference books. As he put it, "the purpose of the NDIRC is to maintain a flow of drug information between the units, not necessarily to reproduce everything."

The NDIRC will coordinate the activities of the peripheral units and will also communicate with regulatory bodies, such as the Food and Drug Board, and other public and private agencies in Ghana. The goal of the NDIRC is to establish a system to facilitate the generation, collection, presentation, and distribution of unbiased drug information throughout the country.

Anum's duties as head of the NDIRC include managing and organizing the center, scanning for new information, providing

training to prospective drug information pharmacists, and developing workplace policies, general quality assurance procedures, and collaborative linkages.

One of Anum's major concerns is the quality of drug information that the NDIRC will provide. To facilitate the training of drug information pharmacists and staff, he has already helped write a basic drug information manual, which discusses the functions of the NDIRC and the peripheral units, staff requirements and job descriptions, reference resources, the systematic approach for answering questions, and legal and ethical issues.

Once the drug information pharmacists and staff have been trained, the NDIRC will begin focusing on ways to incorporate into practice the provision of drug information and the safe use of drugs. More publications will be developed, and training will be expanded to other pharmacists and pharmacy students. This training will include interactive seminars with other health care practitioners from a range of specialties. Training objectives during this phase are to develop the ability of pharmacists to perceive, identify, and appreciate various drug information needs, to adequately and efficiently address these needs using current, relevant, and properly evaluated literature materials, and to document and generate activity reports. For example, the NDIRC plans to train pharmacists to support pharmacy and therapeutics committees and to perform medication use evaluations.

Ultimately, the NDIRC hopes that drug information resources and skills can be used to improve patient care. The NDIRC expects to accomplish this by establishing methods to monitor, describe, and reduce adverse drug reactions; to select and manage cost-effective drugs; to ensure positive, predictive therapeutic outcomes; and to document and report quality-assurance interventions.

The NDIRC considers advocacy a top priority. The necessity, relevance, importance, and acceptability of its services will be promoted at the policy-making level, at the practice level, and at training sites for nursing, medical, and pharmacy students.

After Anum detailed the function of the NDIRC and its plans for the future, he spoke briefly about health care concerns in Ghana and the financial state of the health system there. Anum said he believes that the major issues which health care workers need to focus on are improved sanitation and preventive health. Malaria is seen routinely. Anum said cases of cardiovascular disease and diabetes are on the rise, perhaps because fatty junk food is gradually being incorporated into eating patterns and changes in lifestyle are occurring.

Anum described the current payment system for health care in Ghana as "a cash and carry system with no human face. Those who can pay receive service, and those who cannot pay do without." The previous system in which the government paid for everything failed due to lack of money. The quality under that system varied because, according to Anum, a person might have received a prescription for three medications and only gotten one of them because the pharmacy could not afford to purchase the other two drugs. "The current system is not working

(continued on page 11)

FDA DRUG/BIOLOGIC APPROVALS

Generic Name (FDA Therapeutic Classification) Trade Name	Sponsor (Approval Date)	Valid IDIS Drug Term Drug Number (IDIS Citations)*	Indication/Use	Valid IDIS Disease Term Modified ICD-9-CM Number
Alfuzosin (S) <i>Uroxatral</i>	Sanofi-Synthelabo Inc. (June 12)	ALFUZOSIN 12160407 (40 citations)	Benign prostatic hyperplasia (BPH)	Hyperplasia, Prostate 600.
Alpha-1-proteinase inhibitor (human) (BIOL) <i>Zamaira</i>	Aventis Behring L.L.C. (July 8)	ANTITRYPSIN ALPHA 1- 44100021 (6 citations)	Alpha-1-proteinase inhibitor deficiency and evidence of emphysema	Emphysema NEC 492.
Atazanavir (P) <i>Reyataz</i>	Bristol-Myers Squibb (June 20)	ATAZANAVIR 8180849 (4 citations)	Treatment of HIV-1 virus in combination with other antiretroviral agents	Syn-Acq Immune Deficiency 042.
Emtricitabine (S) <i>Emtriva</i>	Gilead Sciences, Inc. (July 2)	EMTRICITABINE 8180820 (13 citations)	Treatment of HIV-1 virus in combination with other antiretroviral agents	Syn-Acq Immune Deficiency 042.
Ibandronate Sodium (S) <i>Boniva</i>	Roche (May 16)	IBANDRONATE 92600105 (3 citations)	Treatment and prevention of osteoporosis	Osteoporosis 733.0
Omalizumab (BIOL) <i>Xolair</i>	Genentech, Inc.. (June 20)	OMALIZUMAB 82000441 (52 citation)	Asthma	Asthma, Extrinsic 493.0
Palonosetron Hydrochloride (S) <i>Aloxi</i>	Helsinn Healthcare (July 25)	PALONOSETRON 56220029 (2 citations)	Prevention of acute and delayed nausea and vomiting following chemotherapy	Nausea and Vomiting 787.0
Rosuvastatin (S) <i>Crestor</i>	Astra Zeneca (Aug. 13)	ROSUVASTATIN 2406020 (36 citations)	Hypercholesterolemia	Hypercholesterolemia, Pure 272.0
Tositumomab (BIOL) <i>Bexxar</i>	Corixa Corporation (June 27)	TOSITUMOMAB 10120178 (40 citations)	CD positive, follicular, non-Hodgkin's lymphoma	Neop, MGN-Lymph/Histio NEC 202.
Vardenafil (S) <i>Levitra</i>	Bayer Corporation (Aug. 19)	VARDENAFIL 24120102 (11 citations)	Erectile dysfunction.	Impotence, Organic 607.84

* Through August 2003 Update. Complete bibliographic citations will be provided upon request.

** Not applicable.

*** New molecular entity given standard review by FDA.

**** Designated orphan drug.

***** New molecular entity given priority review.

+ Accelerated Approval.

Additional information on these newly approved drugs will be available in the FDA Approval Package [an official United States Food and Drug Administration (FDA) document] that is compiled for new drugs following approval. This document includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are indexed and included as part of the IDIS database. Use descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the database.

New Drugs: Key References

This new drug bibliography provides a selection of key critical studies and reviews of new drugs approved by the FDA May 2003 through August 2003. An *IDIS* search retrieved articles relevant to the new drugs and their approved uses.

Alfuzosin

Ahtoy P, Chretien P, Dupain T, Rauch C, et al. Alfuzosin, an alpha1-adrenoceptor antagonist for the treatment of benign prostatic hyperplasia: once daily dosing in healthy subjects. *Int J Clin Pharmacol Ther*. 2002;40:289-294. (*IDIS* Article Number 483922)

This randomized cross-over study compared alfuzosin dosing 10 mg once daily and 2.5 mg three times daily in 18 healthy males finding bioavailability between the two dosing regimens.

Atazanavir

Sanne I, Piliero P, Squires K, Thiry A, et al. Results of a Phase 2 clinical trial at 48 weeks (AI424-007): A dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naïve subjects. *J Acquir Immune Defic Syndr*. 2003;32:18-29. Pivotal Study (*IDIS* Article Number 492665)

Atazanavir was found to be safe and efficacious at doses of 200, 400 and 500mg once daily, both as monotherapy and in combination with didanosine and stavudine, compared with nelfinavir at 750 mg three times a day in this 48-week randomized trial of 420 HIV-1 infected, antiretroviral-naïve patients.

Emtricitabine

Rosenbach KA, Allison R, Nadler JP. Daily dosing of highly active antiviral therapy. *Clin Infect Dis*. 2002;34:686-692. (*IDIS* Article Number 476868)

This review article compared kinetics and once daily dosing regimens of highly active antivirals for HIV-1 disease and found that once daily dosing of combinations was safe and effective, and also increased patient compliance.

Ibandronate sodium

Papapoulos SE. Ibandronate: A potent new bisphosphonate in the management of postmenopausal osteoporosis. *Int J Clin Pract*. 2003;57:417-422. (*IDIS* Article Number 499742)

Safety and efficacy of ibandronate, given as oral or intravenous dosing in women with postmenopausal osteoporosis, were evaluated in this recent review article.

Omalizumab

Busse W, Corren J, Lanier BQ, McAlary M, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108:184-190. Pivotal Study (*IDIS* Article Number 468002)

This phase III, double-blind, placebo-controlled study randomized 525 patients with severe allergic asthma, and on inhaled corticosteroid therapy, to subcutaneous omalizumab 150 or 300 mg every 4 weeks or 225, 300 or 375 mg every 2 weeks or placebo and found that adding omalizumab reduced asthma exacerbations and reduced the use of inhaled corticosteroids.

Rosuvastatin

Davidson M, Ma P, Stein EA, Gotto AM, et al. Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. *Am J Cardiol*. 2002;89:268-275.

(*IDIS* Article Number 476302)

A double-blind, placebo-controlled trial of 516 hypercholesterolemic patients who were randomized to 12 weeks of once daily dosing of 5 or 10 mg rosuvastatin, 10 mg atorvastatin or placebo found increased LDL cholesterol reduction and increased HDL levels in the rosuvastatin group compared with those in the atorvastatin group.

Tositumomab

Juweid ME. Radioimmunotherapy of B-cell non-Hodgkin's lymphoma: from clinical trials to clinical practice. *J Nucl Med*. 2002;43:1507-1529. (*IDIS* Article Number 488953)

This is an in-depth review of nonmyeloablative doses of Iodine I 131 labeled tositumomab given to patients with B-cell non-Hodgkin's lymphoma in phase I and II multicenter trials in which safety and efficacy of the trial drug were evaluated.



About the Author:

Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a Pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the *IDIS* database, overseeing the Drug and Descriptor vocabulary and contributing articles for the *World of Drug Information* newsletter.

Cognitive dysfunction/severe psychiatric disorders possibly associated with nonsteroidal anti-inflammatory drugs and COX-2 inhibitors in the elderly — more common than we have been led to believe?

Perspective from an



IDIS Subscriber

Recently a 68 year-old male, with no psychiatric history, or other significant medical history, presented with new symptoms of increased memory problems and depression. He had been living alone in the community. His only prescribed medication was ibuprofen 400 mg every 8 hours as needed. On most days he used only one tablet. He denied any over the counter medication use. During the few weeks before admission he might have used more than one ibuprofen daily, but he cannot remember. There was no indication of any acute neurological diagnosis. On admission his ibuprofen was discontinued and sertraline 75 mg daily was begun. Within a few days of his admission the patient considered himself to have returned to his previous functional level. He reported the complete remission of any memory problems or depressive symptoms. He requested to be discharged home. Five days after his admission he was discharged to his home. The only intervention which might explain his rapid recovery is the withdrawal of his ibuprofen. It is unlikely that a few days of sertraline therapy was responsible for his rapid recovery.

Central nervous system dysfunction has been recognized as a complication of the therapeutic use of aspirin in a subset of elderly patients. Several reviews^{1,2,3,4,5} have been published on chronic salicylate intoxication.

One case described by Bailey and colleagues² was a 90 year-old male admitted with a two week history of increasing confusion and falling. One month prior to admission he was living independently and was able to drive a car. His medical history included: osteoarthritis, angina, osteoarthritis, glaucoma and a history of alcoholism. His medications included pilocarpine eye drops, diltiazem, and Extra Strength Bufferin™, six to eight tablets daily.

On admission he was disoriented, unable to give an adequate history, and fabricated some details. His serum salicylate level was 420 mg/L. On admission salicylates were discontinued. By the fourth day his restraints had been removed and he could ambulate with assistance. Because of intermittent falling episodes in the hospital he was discharged to a nursing home for further rehabilitation. His salicylate level had fallen to 69 mg/L prior to discharge.

Another case described by Bailey and colleagues² was a 88 year-old female who was admitted with a syndrome of new onset weakness and confusion. About one month prior to admission she noticed episodes of confusion, nightmares, and slowly progressive weakness. She could no longer care for her debilitated husband. Her medical history included stress incontinence, hypothyroidism and osteoarthritis. Six weeks prior to admission her arthritis medicine had been changed from aspirin to Disalcid™ and the dose had been increased every two weeks. Her medications on admission included Disalcid™ 1500 mg three times daily, sucralfate, doxepin, and thyroid extract. She was unable to rise from her bed unassisted. Her salicylate level was 450 mg/L. Her Disalcid™ was discontinued and she was given diuretics. On the second hospital day she could walk 30 feet with assistance and her endurance improved over the next few days. Her salicylate level on the second hospital day was 15 mg/L. She was discharged home, and with physical therapy she returned to her normal functional level within two months.

Payne reviewed medication related performance deficits with non-narcotic analgesics.⁵ He concluded that central nervous system adverse effects of NSAID's occurred in a significant minority of patients. Those adverse effects included:

headache, dizziness, lightheadedness, vertigo, mental confusion, drowsiness, and visual blurring.

The true incidence of central nervous system adverse effects associated with aspirin, NSAID's and COX-2 inhibitors is unknown. The following reports suggest that they may be more common in elderly patients than clinical trial results would suggest.

The Australian Drug Reaction Advisory Committee⁷ recently summarized 142 reports of acute neuropsychiatric events reported with celecoxib or rofecoxib use. The reported syndromes included: confusion, somnolence, insomnia, hallucination, depression, abnormal thinking and impaired concentration, agitation, and abnormal dreaming and nightmares. In some cases the onset of the reaction was described as "dramatic" and occurred within twenty-four hours of the first dose in 36 cases with celecoxib and in 14 cases with rofecoxib. In 16 cases the reaction occurred again when the patient was rechallenged.

Rothermich⁸ studied the effects of indomethacin in over two hundred clinical trials and on six patients who took part in large dose acute toxicity trials. More than half of the patients on long term indomethacin therapy experienced symptoms of headache, vertigo, light-headedness, and disturbances in sensorium. In 46 patients (20% of 234) the symptoms were severe enough to require discontinuation of or drastic reduction in the dose of indomethacin. The syndromes, whether mild or severe, resolved within a few hours after discontinuation of indomethacin. The central nervous system side effects were dose related and unlikely to appear if the total daily indomethacin dose was no more than 100 mg. However, in a few patients, distressing symptoms occurred with individual doses as low as 25 mg. All six patients who received 300 mg single doses developed violent

headaches, disturbed equilibrium, vertigo, feelings of unreality or dissociation, and disturbance of intellectual acuity. These effects resolved quickly and the drug disappeared from the blood within a few hours.

The New Zealand Medicines Adverse Reactions Committee⁹ received twelve reports of psychological disturbances possibly associated with NSAID use during 1983. These reports included: general lethargy and depression and frank hallucinatory states.

The Australian Drug Reaction Advisory Committee¹⁰ received thirty-one reports of suspected reactions to naproxen from January 1978 to August 1979. Thirteen of the reports provided a description of twenty-four central nervous system symptoms including: headache (5), drowsiness or lethargy (4), dizziness, giddiness or ataxia (4), visual disturbance (4), parasthesia (4), depression (1), insomnia (1), tremor (1), and visual hallucinations (1). They suggested that adverse central nervous system symptoms are not uncommon with all NSAID's, including the newer drugs such as naproxen.

Ames¹¹ described a female patient who told him she stopped taking phenylbutazone for her migraine headaches because it made her "feel so peculiar and I couldn't concentrate or remember. I thought I was losing my mind." A week earlier Ames had heard of two other cases of problems with naproxen and cognitive impairment. The first patient who was taking naproxen 250 mg twice daily, noticed that her recent memory was defective and her ability to conduct familiar activities such as playing bridge was impaired. She did not attribute her symptoms to the naproxen but believed she had become "acutely senile." She had delayed seeing her physician because of her fear of the possibility of being sent to an institution. During this time she attended a regular bridge party. A 60 year-old friend noticed her problems and inquired if she was well. She did not disclose her "mental problems" and said she

had neck and head pain. Her friend said: "Don't take naproxen – my doctor put me on it and I became so disoriented and forgetful that I thought I was losing my mind." The patient stopped the naproxen and within a few days her symptoms disappeared.

Goodwin and Regan¹² published their retrospective study of 40-50 patients who had started taking one of the newer NSAID's during a one year period. They identified 8 patients taking either naproxen or ibuprofen who experienced cognitive dysfunction or personality change after starting the NSAID. None of the patients had significant psychiatric histories or cognitive deficits before beginning their NSAID therapy. In all cases the symptoms cleared within two weeks of stopping the drug. Most complaints were concerned with recent memory problems and or inability to concentrate. Three patients also described symptoms of depression. The patients age ranged from 67 to 82 years. The naproxen doses ranged from 500 to 750 mg daily and the ibuprofen doses from 1600 to 8200 mg daily. The majority of these patients did not report their symptoms for fear of being identified as "senile." The group expressed relief when told the medication could cause these changes in their mental status and would most likely resolve within days or a few weeks of stopping the medication. They also noted they had seen similar cognitive changes in three patients younger than 65 years old. They recommend informing the patient about the possibility that the NSAID could cause cognitive and mood changes. For monitoring new NSAID patients they suggest a simple mental status exam and direct questioning about any new cognitive problems. They concluded that memory loss, inability to concentrate, confusion, and personality change are common toxic syndromes of the newer NSAID's in elderly patients.

Severe acute onset psychiatric side effects were

reported with indomethacin shortly after it's introduction. Included were two cases of psychosis with indomethacin.¹³ Symptoms of paranoid delusions, depersonalization, and hallucinations began within a short time after starting indomethacin and cleared rapidly after the drug was discontinued. There have also been two reports of toxic psychosis attributed to sulindac.^{15,16}

Browning¹⁷ published a case series of four psychiatric outpatients whose pain was treated with NSAID's. All four patients developed moderate to severe depression and one became severely paranoid while on NSAID's. Onset of the toxic syndrome varied from one day to a week after therapy was initiated. Antidepressants prescribed while the patients were receiving the NSAID's appeared ineffective in preventing or treating the depression.

Katz and colleagues¹⁸ described a 27 year-old paranoid schizophrenic with a four year psychiatric history who experienced exacerbation of his disorder after short term ibuprofen use. The patient was in remission and living at home on a stable regimen of risperidone 2 mg daily. He was instructed to take 200 mg of ibuprofen for backache (two in the evening and one in the morning). By noon of the following day he had feelings of grandeur and paranoid and bizarre delusions. He had no perceptual disturbances. He took one additional ibuprofen and a short time later he experienced extreme aggravation. After an emergency consult with his psychiatrist he discontinued the ibuprofen. Within forty-eight hours his psychotic symptoms had resolved.

Mallet and colleagues¹⁹ described behavioral problems in an elderly demented patient after six doses of indomethacin 25 mg. The patient became very agitated, confused, and was physically and verbally aggressive to hospital staff.

After withdrawal of the indomethacin and treatment with haloperidol 0.5 mg daily, the syndrome cleared within ten days.

Bernstein and colleagues²⁰ described a 76 year-old male with normal mental status, who became confused, was lost in familiar places, and had short term memory loss after beginning ibuprofen 600 mg three times daily for osteoarthritis. The syndrome began within one week of starting ibuprofen and completely resolved within one week of stopping the drug. The pattern was repeated 6 months later. There was no apparent alternative cause for either the first or second syndromes.

Other risk factors for these syndromes include dose increases, higher than normal daily doses, and use of multiple drugs in the class for different purposes. You may wish to explain to your patients who are beginning therapy with NSAID's or COX-2's that these syndromes might occur. Their incidence is unknown but they are thought to occur infrequently. The syndromes will clear within days or a week or two of discontinuing the offending drug.

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2004 RENEWAL REMINDER

2004 IDIS subscription renewal notices will be sent in September. We urge you to notify us of your renewal intentions as soon as possible. To avoid interruption of service, we need to receive your renewal form by January 1, 2004. Thank you for your prompt attention to your 2004 IDIS subscription renewal.

(continued from page 6)

either, so pilot insurance programs are being tested," Anum said.

Anum's position as the coordinator for the NDIS and the head of the NDIRC in Ghana is what led him to DDIS. Originally, he had been looking for a consultant to come to Ghana to help establish the NDIRC and to assist with the training of the drug information pharmacists. A clinical pharmacist in Ghana told him about DDIS, so he contacted the director, Hazel Seaba. Seaba suggested that it might be best if Anum came to DDIS so that he could receive training at an established drug information center and get a better idea of how it functioned.

"Every day is something new," Anum said during his training at DDIS. After an orientation period, he received training in promoting a drug information service, educating students, establishing a database, evaluating drug literature, writing and publications, and informatics. He also received training at the University of Iowa

Hospital Drug Information Center, where he was exposed to the pharmacy and therapeutics committee, drug safety, medication use evaluation, investigational drug studies, and quality assurance. During his last week at DDIS, he attended the American Association of Colleges of Pharmacy annual meeting in Minneapolis. At the end of his training, he presented a seminar to the DDIS staff on Ghana's strategy for improving medication safety through comprehensive drug information.

Anum additionally said that the visit to DDIS gave him "better insight into what goes into primary literature indexing." He spent time with each person involved in the production of the *Iowa Drug Information Service (IDIS)* database. "I was very impressed with seeing how the indexing is done, the quality of the materials, and what goes into indexing," he said. He found the discussion of the descriptors particularly useful. "The descriptors are filters that you can use to separate the information you want from the junk," as he called it. He

suggested that organizations explore the IDIS database with a trial subscription and consider purchasing a permanent subscription. As Anum explained, the IDIS database is a good investment because "it contains a lot of information in one system."

"I would recommend DDIS training to others," Anum said. "It has given me a chance to see the details and activities involved in the operation of an established drug information center and to identify the limitations of what the NDIRC in Ghana will be able to do. I have seen a lot of things that my organization can incorporate, such as medication use evaluations and a link between drug information departments and P&T committees." Anum concluded, "I have seen the situation. When I return to Ghana, my job will be to apply the information that I have learned."

Customized, flexible training at DDIS is available to any practicing pharmacist (<http://www.uiowa.edu/~idis/education.htm>). The two- to twelve-week program includes a

EDITORS NOTE:

FROM TIME TO TIME, WE PUBLISH ARTICLES CONTRIBUTED BY IDIS SUBSCRIBERS. AN ARTICLE FROM DAVE MACE, B.S.PHARM., IS INCLUDED IN THIS ISSUE. DAVE MACE IS FROM AN INSTITUTION THAT IS A LONG-STANDING IDIS SUBSCRIBER, UTILIZING THE DATABASE ON A REGULAR BASIS. HIS CONSULT ILLUSTRATES IDIS DATABASE USE CONTRIBUTING DIRECTLY TO PATIENT CARE OUTCOMES. THE RESPONSIBILITY FOR ERRORS IS THE AUTHOR'S ALONE. THE CONSULT DOES NOT NECESSARILY REPRESENT HOSPITAL VIEWS AND RECOMMENDATIONS. WE HOPE YOU FIND THE INFORMATION INTERESTING AND USEFUL AND WELCOME COMMENTS. IF YOU ARE INTERESTED IN SHARING YOUR EXPERIENCES USING THE IDIS DATABASE, PLEASE CONTACT DONNA-BRUS@UIOWA.EDU

About the Author:

Dave Mace, R.Ph., Drug Information Specialist, wrote the article. Mace graduated from the University of Iowa College of Pharmacy in 1967. Since 1982 he has served as the Director of the Drug Information Center at BPVAMC, 10,000 Bay Pines Blvd., Bay Pines, FL 33744. His responsibilities include serving as a preceptor for drug information and Pharm.D. clerkship programs and responding to complex drug information requests from clinical staff.

combination of lectures, readings, discussions, assignments, participation in ongoing projects, verbal and written presentations, and experiential training in a university and hospital setting. The World Health Organization (WHO) has funded fellowships for this training; the regional WHO office should be contacted for details and a program application. For additional information on program fees and arrangements, please contact DDIS.

About the Author:

Vicki Kee is a 1989 graduate of the University of Alabama at Birmingham (B.A. in English) and a 1999 graduate of Samford University College of Pharmacy (Pharm.D.). She completed a drug information residency at Idaho State University College of Pharmacy in 2003 and then joined the Division of Drug



Information Service (DDIS) at the University of Iowa College of Pharmacy. Vicki is a contributing author to the *World of Drug Information* newsletter, assists with answering drug information inquiries made to the Iowa Drug Information Network (IDIN), teaches drug information to pharmacy students and indexes journal articles for inclusion into the IDIS database.

(continued from page 4)

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DDIS EXHIBIT SCHEDULE 2003

American College of Clinical Pharmacy
2003 Annual Meeting
November 2-5, 2003
Hyatt Regency Atlanta
Atlanta, GA
Booth #212

American Society for Health-System
Pharmacists
39th Midyear Clinical Meeting
December 7-11, 2003
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