North Carolina Rheumatology Association
Position Statements

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I-A: Appropriate Delivery, Handling, Storage and Administration of Biologic Agents

Statement: **The North Carolina Rheumatology Association believes that the standard of care for the administration of biologic agents for autoimmune inflammatory rheumatic diseases requires rheumatologist recommendations for the choice of medication as well as rheumatologist approval of the handling, delivery, storage and administration of intravenously administered medications when infusions are performed in their offices**.

Discussion: In the last decade there have been numerous discoveries that have lead to a better understanding of the pathogenesis of rheumatoid arthritis. As a result of these discoveries, agents that modify specific abnormalities of the immune system, termed biologic agents, have been developed. The use of these agents in the treatment of rheumatoid arthritis and other autoimmune diseases has resulted in a marked improvement of the overall condition of people with these illnesses. According to some studies it is now possible to even prevent deformities and resultant disabilities in illnesses like rheumatoid arthritis.

Biologic agents target interleukins and cytokines, which are involved in disease pathogenesis and inflammation. For the treatment of rheumatoid arthritis the FDA has approved the use of infliximab, etanercept, anakinra and adulimumab. These medications have been shown, in clinical trials, to have a dramatic impact on disease activity by reducing joint swelling, pain, and stiffness. Several of these medications (infliximab, etanercept and adulimumab) have additionally been shown to reduce joint erosions and joint space narrowing which lead to joint destruction, deformities and disability. Use of these agents not only improves short-term disease activity and symptoms but also improves long-term outcomes by preserving quality of life, decreasing disability and avoiding the need for joint replacement surgery and perhaps even long term care.

There are many therapeutic alternatives for the treatment of rheumatoid arthritis. A rheumatologist, with patient involvement, must consider age, gender, length and severity of illness, and other medical history in determining the appropriate medication for that specific patient. **The North Carolina Rheumatology Association believes that the choice of biologic agents for the treatment of rheumatoid arthritis is the responsibility of the treating rheumatologist and the patient based on standard of care issues. Additionally, in-office infusion of intravenous biologic agents is extremely safe and highly cost-effective <u>in the hands of rheumatologists</u>.** This is similar to the current policies established for physicians specializing in Oncology, who have been utilizing in-office infusion of chemotherapy for many years.

These medications require appropriate handling and delivery. Without appropriate refrigeration and handling, these medications can be denatured or damaged. If denatured, more serious side effects may occur during infusion or administration. It is therefore imperative that the delivery of these medications also remains acceptable to established standards of care for biologic agents. This is of extreme importance in biologic agents requiring intravenous infusion.

The intravenous infusions of biologic agents can be associated with potentially serious side effects, including: pruritus, rash, headache, dyspnea, chest pain, hypertension, hypotension and even anaphylactic reactions. It is imperative that this medication be given in a controlled environment with experienced staff present knowledgeable of the patient's complicated medical history, aware of the potential side effects of the infused biologic agents and competent in the management of potential adverse events. Under these conditions, patient acceptance and confidence is increased, compliance is assured, outcomes are optimized and efficiency is maximized.

I-B: Biologic Agents – Indications for Use

Statement: **The North Carolina Rheumatology Association believes that the use of biologic agents (infliximab, etanercept, anakinra and adulimumab) for the treatment of patients with serious autoimmune diseases (e.g. psoriatic arthritis, ankylosing spondylitis, inflammatory eye disease, Behcet's disease) is appropriate in those who do not respond to other therapies or are not candidates for other therapies available and is the standard of care when patholophysiologic evidence and published information for efficacy exists and supports the use of these agents. To interfere with this prudent, reasonable and cautious treatment of patients represents an interference with the standard of care for patients in need of serious disease treatment in a timely manner These treatments should be quickly approved and available through health insurers when a rheumatologist has concluded that treatments with these agents are necessary.**

Discussion: In the last decade, increased knowledge of cytokine activation and interactions has lead to a better understanding of the pathogenesis of rheumatoid arthritis, psoriatic arthritis, and other autoimmune inflammatory diseases. As a result of these discoveries and the development of biologic agents to inhibit cytokine activities, a marked improvement in control and prevention of progression is now possible in many diseases. FDA approval of these and other medications for specific indications are recognized as guidelines for the pharmaceutical industry and are not intended to restrict medical use where appropriate. Pathophysiologic mechanisms in other serious, uncommon and rare diseases warrant use of these agents especially where academic experience, published information and/or scientific information is confirmatory.

For example, infliximab (Remicade) and etanercept are biologic agents targeting tumor necrosis factor, a key cytokine in immune mediated inflammatory diseases. The FDA has approved these agents for use in the treatment of rheumatoid arthritis, psoriatic arthritis and, in the case of infliximab, for Crohn's disease. Other indications are pending FDA approval. This medication has been shown in numerous clinical studies, as published in scientific journals and published at scientific meetings, to have a dramatic impact on the disease activity of many other conditions not responsive to other therapies including psoriasis, ankylosing spondylitis, inflammatory eye disease, Reiter's syndrome and Behcet's syndrome. Improvement in joint, skin and destructive organ involvement is observed in these respective diseases when treated with infliximab. Improvement in short-term disease activity with preservation of function, low risk and long-term quality of life (potentially resulting in less disability, decreased need for joint replacement surgery, decreased skin scarring, preservation of vision and probably decreased mortality due to other disease complications and comorbid conditions) are possible with these treatments (references available upon request).

Biologic agents need to be available when therapeutic alternatives for the treatment of psoriasis, psoriatic arthritis, ankylosing spondylitis, inflammatory eye disease, and Behcet's disease fail or are not indicated. The FDA has approved the use of etanercept for the treatment of psoriatic arthritis however availability has not been reliable. No other biologic agents have received FDA approval for treatment of psoriasis, ankylosing spondylitis, autoimmune inflammatory eye disease, or Behcet's disease. Infliximab has been shown in many clinical studies to have significant benefit in psoriasis, ankylosing spondylitis, inflammatory eye disease, and Behcet's disease.

A rheumatologist, with the agreement of the patient, must consider a patient's age, gender, length and severity of illness, potential complications of alternate therapies, comorbid conditions and other medical history in determining the appropriate medication for management. To abrogate or impair this decision making capacity of Rheumatologists is indicative of a denial to accept the standard of care as set forth by the North Carolina Rheumatology Association.

II-A. Osteoporosis Treatment in patients unable to tolerate routine therapy

Statement**:** **The North Carolina Rheumatology Association recommends that intravenous bisphoshonate therapy, when prescribed by rheumatologists after thorough evaluation, be available, utilized and appropriately reimbursed by health insurers for the treatment of osteopenia, osteoporosis, and/or low-trauma fractures (fragility fractures), in appropriate patients who cannot tolerate or are refractory to treatment with estrogen replacement therapy, raloxifene (Evista), alendronate (Fosamax) or risedronate (Actonel). Use of parenteral bisphoshonates is also not inappropriate in these same patients after successful treatment with teraperitide. We believe that this represents the standard of care for these seriously ill patients.**

Discussion: The *NIH Consensus Statement on Osteoporosis Prevention, Diagnosis, and Therapy* defines osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality." Osteoporosis is a silent disease until bones become so weak that fractures occur. Osteoporosis is a major health problem in the United States, affecting approximately 10 million people. Approximately 18 million people have osteopenia. One of every three women over the age of 50 have osteoporosis and nearly half of all women over 50 will break a bone in her lifetime due to osteoporosis. Approximately one in every eight men over the age of 50 will have an osteoporotic fracture in his lifetime. Ultimately, in an extremely elderly population, one in every six men will have a hip fracture.

Appropriate therapeutic alternatives for the prevention and treatment of osteoporosis include calcium, vitamin D, estrogen replacement therapy, raloxifene (Evista), alendronate (Fosamax), risedronate (Actonel), calcitonin (Miacalcin) and teraperitide (Forteo). Unfortunately, some patients have contraindications to taking these medications, develop intolerable side effects, or are refractory to therapy. An alternative to these routine medications is intravenous bis-phosphonate therapy, such as pamidronate (Aredia). Pamidronate has been shown to inhibit bone resorption and improve bone density in patients with osteoporosis.

II-B. Osteoporosis Evaluation in Men

Statement: **The North Carolina Rheumatology Association recommends that central DEXA studies be performed and appropriately reimbursed by insurance, for these additional conditions: 1) testosterone deficiency (257.2?); 2) men over the age of 70 (code?); 3) men receiving hormonal therapy for the treatment of prostate cancer (V58.69?); 4) men with any low trauma fracture (codes?); and 5) men with rheumatoid arthritis (714.0) and other autoimmune inflammatory diseases.**

Discussion: The *NIH Consensus Statement on Osteoporosis Prevention, Diagnosis, and Therapy* defines osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality." Osteoporosis is a silent disease until bones become so weak that fractures occur. Osteoporosis is a major health problem in the United States, affecting approximately 10 million people -20% of who are men. Approximately 18 million people have osteopenia –approximately 20% of who are men. Thirty percent of all hip and vertebral fractures occur in men. Approximately one in every eight men over the age of 50 will have an osteoporotic fracture in his lifetime. Ultimately, in an extremely elderly population, one in every six men will have a hip fracture.

Osteoporosis in men has become a major health problem as the elderly population expands. In men, bone density declines slowly after 30 years of. A number of risk factors increase the chance of developing osteoporosis and fractures in men, including: smoking, excessive alcohol consumption, the use of corticosteroids and certain anti-seizure medications, inadequate intake of calcium and vitamin D, inadequate exercise, a family history of osteoporosis, and a previous history of low trauma fracture (hip, wrist, pelvis, etc.). Illnesses such as hyperthyroidism, hyperparathyroidism, and severe liver and kidney diseases can lead to osteoporosis. In men, the lack of testosterone and the use of some treatments for prostate cancer (e.g., Lupron) can also result in osteoporosis. Additionally, rheumatoid arthritis can increase bone resorption and can lead to metabolic bone disease.

Osteoporosis, in both men and women, is best diagnosed with a central bone density test, called a DEXA. Although both central and peripheral bone density tests can identify patients with osteoporosis or osteopenia, central DEXA studies are recognized as the only way to monitor response to therapy. Moreover, the World Health Organization definitions of disease prevalence using T-score equivalents are based on central, not peripheral, DEXA measurements.

Medicare and other insurance companies generally cover central DEXA studies in men for the following diagnoses: osteopenia (733.90), osteoporosis (733.00 – 733.09), hyperparathyroidism (252.0), vertebral fracture (733.13), or for monitoring of bone density when on chronic corticosteroids (V58.69) or monitoring response to therapy (V67.59).

III. Cox-2 Drugs

Statement: **It is inappropriate to apply the same restrictions, review processes and scrutiny to subspecialty Rheumatologists prescribing Cox 2 or other NSAID medications as those used to review, restrict or scrutinize other specialists. The North Carolina Rheumatology Association strongly recommends alteration of the review processes and restrictive processes for Rheumatologists prescribing any and all anti-inflammatory agents for the care of patients with serious inflammatory rheumatic diseases. To continue to do otherwise is counter-productive, costly, inappropriate and harmful to patient care.**

COX 2 anti-inflammatory medications represent a significant advance in rheumatology therapeutics with markedly decreased GI toxicity compared to previously available agents. Appropriate selection of anti-inflammatory agents for chronic uses in inflammatory rheumatic diseases is complicated given other existing comorbid conditions, use of concomitant medications prescribed by other physicians, patient age and patient debility. This medical decision making process differs significantly from NSAIDs selection for short-term use in acute musculoskeletal traumas and injuries, minor, short term arthritic problems or for other non-rheumatic purposes by other specialists.