

Medication Safety in Children with Arthritis

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Chronic arthritis affects approximately 1 out of 1000 children, many of whom will be affected into their adulthood.¹ Over the past decade the advent of potent biological therapies such as tumor necrosis factor-alpha (TNF-alpha) antagonists has altered our expectations for the outcomes of polyarticular arthritis for the better. It is now rare to see arthritis leave a child wheelchair-bound, and measures such as serial casting and bracing to treat fixed joint flexion contractures are now infrequently needed. These advances are due in part to maturation of the field of pediatric rheumatology but also due in large part to available therapeutic options that are more effective than were the agents used in the past. However, by virtue of their novelty, these biologic medications lack much data on long-term safety. The safety data are limited in adults, and they are even sparser in children given smaller numbers of patients, less data collection, and fewer studies performed. When we consider that individuals affected with chronic arthritis from childhood will be exposed to various immunomodulatory and other medications (eg, nonsteroidal anti-inflammatory drugs, nonbiologic disease-modifying antirheumatic drugs) over the course of many years, it is important to be systematic in our study of the possible long-term side effects in children. Extrapolating from adult studies is inadequate because there are unique safety considerations in children.

Lack of safety data for medications in children is not confined to novel biologic therapeutics. In the past the lack of systematic drug testing in pediatric therapeutics has resulted in widespread off-label use—across primary and specialty care—of an estimated 75% of medications and well-publicized examples of resultant harm done to children.² Despite the knowledge that children are not little adults in terms of therapeutic regimens, it has long been practice to treat children with medications studied only in

adults by adjusting dosage for weight. Due to differences in pharmacokinetics and the added complexity of metabolism changes with age, growth, and development, treatment of children based on studies in adults could result in harm from underdosing and exposing patients to potential side effects without therapeutic benefit, from potentially overdosing, or from unknown pediatric-specific adverse effects.³

Recent legislation has stimulated and mandated more widespread testing in children. The Best Pharmaceuticals for Children Act of 2002 and the Pediatric Research Equity Act of 2003 were recently reauthorized for another 5 years as Public Law 110-85.⁴ The first act creates an incentive for pharmaceutical companies to study existing medications in children by granting an additional 6 months of marketing exclusivity (ie, pediatric exclusivity).⁵ The Pediatric Research and Equity

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Act requires drug manufacturers applying for a new product or new product indication to submit data on testing the product in children. These acts served to expand the knowledge of appropriate medication use in children with subsequent pediatric label changes for over 130 medications resulting from the Best Pharmaceuticals for Children Act⁶ and more than 60 new listings resulting from the Pediatric Research and Equity Act.⁷ The Best Pharmaceuticals for Children Act also has resulted in mandatory study of adverse events specific to children for 12 months postexclusivity which has provided some new information on pediatric-specific adverse events.⁸

The resultant increase in clinical trials for pediatric patients spurred by these legislative acts has implications for the practice of rheumatology. They have expanded the evidence base with which to prescribe and set expectations of therapeutic effectiveness. The successful pursuit of clinical trials in pediatric patients also has practical implications from the standpoint of being able to seek

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insurance coverage for therapeutics that have a pediatric indication. Even so, the challenge to conduct pediatric rheumatology clinical trials remains daunting. The relative rarity of these conditions in children generally requires a multisite, multinational effort over a lengthy enrollment period to reach sample sizes necessary to adequately power a study. Despite the best of planning, this may still result in a negative study. For example, a recent clinical trial of the TNF-alpha antagonist infliximab in juvenile rheumatoid arthritis failed to reach the primary endpoint despite the apparent benefit observed in the clinical practice setting.⁹ Such a frustration does not mean that similar studies should not be performed, but rather that the pediatric rheumatology research community needs to redouble its efforts in the conduct of randomized clinical trials of novel therapeutics with improved study design and identification of more effective trial endpoints.

Treating children with arthritis on the basis of studies in adults is not sufficient and arguably not ethical. Just as children are not small adults, rheumatoid arthritis is a distinct entity from the various forms of childhood arthritis.¹⁰ In addition to studying results of drug manufacturers' 12-month safety extension of clinical trials under pediatric exclusivity, it behooves pediatric rheumatologists to pursue independent means of better assessing medication safety through the development of safety registries to capture larger numbers of treated patients, to promote more systematic adverse event reporting through the Food and Drug Administration Med Watch system (www.fda.gov/medwatch), and to conduct studies of administrative claims data for evidence of adverse events as has been done in several studies of TNF-alpha antagonists safety in treatment of adult rheumatoid arthritis.¹¹⁻¹³

When information was released on the adverse cardiovascular risk profile of the selective Cox-2 inhibitor VIOXX in adults and it was withdrawn from the market (ironically just 6 weeks after its approval for treatment of juvenile rheumatoid arthritis), there were few data to provide parents about long-term cardiovascular risk in children. The reply in response to questions about possible ill effects of these medications with long term use, "There have been no such reports in children," while true to the best of our knowledge is not a rigorously studied answer. For this reason, once childhood arthritis is under control, it is often a goal of the pediatric rheumatologist to try and taper off systemic medications in order to limit cumulative exposure.

From the standpoints of the individual primary care provider, parent, and pediatric rheumatologist, there are practical steps to advance safe medication use in children with arthritis. One of the key steps to promoting patient safety in children with arthritis is a strong partnership between the prescribing rheumatologist and the child's primary care provider. There are 3 primary threads to this relationship. First, collaboration to ensure patient compliance with routine laboratory testing (often performed locally every 4-8 weeks) to monitor for medication toxicity¹⁴ and communicating these results to the rheumatologists for review; second, maintenance of up-to-date immunization status including yearly influenza vaccination with inactivated virus vaccine (live vaccines are currently contraindicated in

Information on Arthritis in Children:

Readers interested in more information on arthritis in children or specific therapeutics are encouraged to consult the Web resources listed below. The Pediatric Education Drug Safety (PEDS) project underway at the University of North Carolina at Chapel Hill (UNC) is developing online continuing medical education for primary care providers along with downloadable provider resources. One of 3 PEDS modules is devoted to medication use and safety in childhood arthritis. The resource will be free to all and available in 2008 (<http://harryguess.unc.edu/index.htm>).

Web Resources:

UNC PEDS:

<http://harryguess.unc.edu/index.htm>

American College of Rheumatology:

<http://www.rheumatology.org/>

Arthritis Foundation:

<http://www.arthritis.org/index.php>

Childhood Arthritis & Rheumatology Research Alliance:

<http://www.carragroup.info/>

Food and Drug Administration Pediatric Drug Development:

<http://www.fda.gov/cder/pediatric/index.htm>

MedWatch:

<http://www.fda.gov/medwatch/index.htm>

children on immunosuppressive medications);¹⁵ and third, prompt evaluation and treatment of patients on immunosuppressant medications who present with suspected bacterial infection due to the decreased ability to contain the infection.

The partnership between primary care providers and rheumatologists extends in other ways. For example, in some cases the primary care provider's office administers subcutaneous injection arthritis medications for the patients where the parent or guardian is unable. This partnership in care is particularly important in our state because many patients travel long distances across North Carolina to see a pediatric rheumatology specialist located at an academic medical center. The local medical provider will be the first responder to these children in case of infection or disease flare. Good communication between the local treating physician and the pediatric rheumatologist in the care of children with arthritis is invaluable.

The partnership extends to patient education, acceptance of the diagnosis, and comfort with the treatment plan. Pediatric rheumatologists face hurdles with new patients. They begin with overturning the misconception that the child will simply outgrow the arthritis. When parents arrive with this notion, it takes some convincing to explain that medication is indicated and that the known benefits of averting disability and pain from untreated arthritis outweigh the potential risks, some of

which are unknown. The primary care provider may use the trust resultant from a long-term relationship with the family to help cope with the diagnosis and facilitate care.

The family may be preoccupied by the child's pain, worried by his or her present functional limitations, and concerned that the child is standing on the sidelines instead of participating with peers. Although they may be eager for their child to get better, many parents are anxious about giving their child any medications because they fear side effects, although not infrequently these same individuals may administer a host of natural supplements that are not regulated or scientifically tested. Time and care are necessary for patient education. It is important to review the medications, indications, the administration process, known and potential side effects, and toxicity monitoring. This helps make the family more comfortable with the treatment plan and enhances compliance. In rare instances parents have reported that the pediatrician told them the medications prescribed by the rheumatologist for arthritis are too strong for a child and advised against taking them. On occasion even some pharmacists have told parents their child should not have been prescribed a medication recommended by the rheumatologist.

As a pediatric rheumatologist, I would rather discuss the rationale for prescribing a medication with the pharmacist or local care provider than have a child return to the office for his or her follow-up appointment with untreated ongoing inflammation, risking permanent joint damage. Partnership along the chain of medical care will result in more effective treatment.

The future is bright in arthritis care. Increasing numbers of new therapeutics will be available, particularly new biologic therapeutics currently under development. Indeed, a number of emerging biologic treatments studied in arthritic adults remain to be studied in children. It is imperative that clinical trials proceed in children to ultimately allow for evidence-based rather than experimental medication use in children. Until we routinely and systematically collect safety data on children using medications for arthritis, we will be left with anecdotal reports, the lowest level of scientific evidence. **NCMJ**

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REFERENCES

- Oen K, Malleson PN, Cabral DA, Rosenberg AM, Petty RE, Cheang M. Disease course and outcome of juvenile rheumatoid arthritis in a multicenter cohort. *J Rheumatol*. 2002;29(9):1989-1999.
- Roberts R, Rodriguez W, Murphy D, Crescenzi T. Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. *JAMA*. 2003;290(7):905-911.
- Roberts, R. What's So Special About Children? Presented at the American College of Toxicology 22nd Annual Meeting; November 6, 2001; Washington, DC. http://www.fda.gov/cder/pediatric/presentation/tox_peds_nov2001/index.htm.
- Food and Drug Administration Amendments Act of 2007. <http://thomas.loc.gov/cgi-bin/query/z?c110:H.R.3580>. Accessed September 28, 2007.
- Li JS, Eisenstein EL, Grabowski HG, et al. Economic return of clinical trials performed under the pediatric exclusivity program. *JAMA*. 2007;297(5):480-488.
- Pediatric Exclusivity Labeling Changes as of August 8, 2007. US Food and Drug Administration. Center for Drug Evaluation and Research Web site. <http://www.fda.gov/cder/pediatric/labelchange.htm>. Accessed October 14, 2007.
- PREA Labeling Changes as of August 8, 2007. US Food and Drug Administration. Center for Drug Evaluation and Research Web site. http://www.fda.gov/cder/pediatric/Prea_label_post-mar_2_mtg.htm. Accessed October 14, 2007.
- Summaries of Medical and Clinical Pharmacology Reviews of Pediatric Studies as of October 1, 2007. US Food and Drug Administration. Center for Drug Evaluation and Research Web site. <http://www.fda.gov/Cder/pediatric/summaryreview.htm>. Published June 18, 2003. Updated October 2, 2007. Accessed October 14, 2007.
- Ruperto N, Lovell DJ, Cuttica R, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum*. 2007;56(9):3096-3106.
- Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol*. 2004;31(2):390-392.
- Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. *Arthritis Rheum*. 2007;56(4):1125-1133.
- Setoguchi S, Solomon DH, Weinblatt ME, et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. *Arthritis Rheum*. 2006;54(9):2757-2764.
- Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis Rheum*. 2004;50(2):372-379.
- Newsome G. American College of Rheumatology. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum*. 2002;46(2):328-346.
- American Academy of Pediatrics. Immunizations in Special Clinical Circumstances. In: Pickering L, Baker CJ, Long SS, McMillan JA, eds. *Red Book: 2006 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2006: 71-78, 85-87.