

Progress in pediatric rheumatology: apprehend the opportunities of the future without forgetting the lessons from the past

Hans-Iko Huppertz · Dirk Föll · Hermann Girschick ·
Kirsten Minden · Gerd Horneff

Received: 12 July 2011 / Accepted: 20 July 2011 / Published online: 8 September 2011
© Springer-Verlag 2011

What you have inherited from your fathers, acquire it
in order to possess it

[Was du ererbt von deinen Vätern hast, erwirb es, um
es zu besitzen]

Goethe
Faust

Juvenile idiopathic arthritis (JIA), the most frequent chronic inflammatory disease in children and adolescents, is defined by the most accurate description of seven exclusive subtypes [1]. In contrast, the latest classification criteria for rheumatoid arthritis (RA), a joint project by the European League against Rheumatism (EULAR) and the American

College of Rheumatology (ACR), describe the disorder by criteria that compel the attending rheumatologist to prescribe a disease-modifying antirheumatic drug, mostly methotrexate [2]. Investigators mainly from North America and endorsed by the ACR have chosen a similar path by defining treatment groups for JIA and giving recommendations for the treatment of JIA [3]. Beukelman and coinvestigators first assembled the relevant literature excluding review articles between 1966 and 2009 and found 221 articles that were reviewed and abstracted by a group of experts. Since differential treatment between the different categories of JIA is not established, the authors developed treatment groups that are in part similar to older categories of pediatric rheumatic disorders including oligoarthritis, polyarthritis, sacroiliac arthritis, systemic arthritis with systemic features and systemic arthritis with arthritis. For each category, they defined features of poor prognosis and three levels of disease activity. Finally, the authors created 1,539 clinical scenarios with a given treatment group and history of treatment and description of disease activity and prognosis. All these scenarios were evaluated individually by each member of a task force of experts, practitioners and a parent and assessed for the appropriateness of initiating a certain treatment option. The expert group then translated the results into text and finally determined the level of evidence of each recommendation. The authors added algorithms for four of the five treatment groups. Beukelman et al. have undertaken a gigantic project and achieved an unparalleled step ahead in the development of pediatric rheumatology.

Already in the introduction, the authors admit that they did not consider indications for systemic glucocorticoids for the treatment of synovitis since they could not find any published evidence [3]. This is a remarkable statement since generations of pediatric rheumatologists have relied on the administration of systemic glucocorticoids and were

H.-I. Huppertz (✉)
Klinikum Bremen-Mitte, Bremen and Children's Hospital,
University of Göttingen, Göttingen, Germany
e-mail: huppertz.bremen@t-online.de

D. Föll
Department of Translational Inflammation Research,
Institute of Immunology, University of Muenster,
Münster, Germany
e-mail: dfoell@uni-muenster.de

H. Girschick
Klinik für Kinder- und Jugendmedizin,
Klinikum am Friedrichshain, Berlin, Germany
e-mail: Hermann.Girschick@vivantes.de

K. Minden
Department of Pediatric Rheumatology,
Charité University Medicine Berlin, Berlin, Germany
e-mail: kirsten.minden@charite.de

G. Horneff
Asklepios Children's Hospital, Sankt Augustin, Germany
e-mail: g.horneff@asklepios.com

and are experts in using the beneficial antirheumatic properties while avoiding the adverse effects.

In fact, there are several reasons to question the appropriateness of excluding systemic glucocorticoids from the treatment of arthritis in children with JIA.

- It is textbook knowledge that synovitis is amenable to treatment with systemic glucocorticoids including a long record of efficacy and adverse effects. The vast knowledge of adverse effects of glucocorticoids and the "intelligent" use of glucocorticoids for the benefit of the patient while avoiding the unwanted effects are proof of the extensive knowledge of efficacy. Intelligent use of glucocorticoids includes topical administration such as intra-articular glucocorticoids (which are being accepted by Beukelman et al.), low-dose glucocorticoids, which implies the avoidance of cushingoid side effects, and glucocorticoid pulse therapy which may be repeated after a few weeks without the occurrence of long-term adverse effects [4]. So, there is ample knowledge on the treatment of arthritis with systemic steroids, but this predates the introduction of controlled trials.
- There is good evidence for the appropriateness of using several biological DMARDs because these new substances were required to demonstrate effectiveness in controlled trials prior to obtaining an FDA/EMA license for children. Such randomized placebo-controlled trials are costly, and there is no financial incentive to test how the oldest antirheumatic drug on the market, glucocorticoids, could be most reasonably used. Consequently, the authors' path favors new costly therapies and neglects old inexpensive treatments such as glucocorticoids that have been available for decades.
- Glucocorticoids can be administered in various ways, i.e., oral, i.v., local, the dosage per kg body weight and the distribution of the doses over the day, the duration of treatment (days, weeks or months) and the repetition of treatment as in pulse therapies vary widely and many regimens have been described as being effective. These extreme variations render handling of this drug in the authors' project very difficult if not impossible. However, if a probably very valuable drug cannot be assessed by an analytical method, the consequence should be to admit this methodological problem rather than the exclusion of the drug.
- The authors do not discuss the concept of glucocorticoids as a bridging agent. Systemic glucocorticoids render rapid relief to patients with polyarthritis during the period from initiation of slowly acting drugs including methotrexate till the onset of their efficacy.
- The actual algorithms for the treatment of polyarticular JIA include the administration of systemic glucocorticoids. In fact, all recent controlled studies allowed for the

administration of low-dose glucocorticoids [5]. If the authors believe glucocorticoids are not necessary, they should have recommended testing their new approach against standard treatment, i.e., methotrexate + glucocorticoids versus methotrexate alone or versus methotrexate + early introduction of TNF- α -blocker rather than excluding glucocorticoids.

- The concept proposed by the authors argues for the early introduction of biological DMARDs including TNF- α -blocker [3]. The therapeutic efficacy and the safety record of these drugs are impressive. However, the unresolved debate on the rare, but possible induction of malignant lymphoma due to administration of TNF- α -blockers should remind us of the necessity of continuing vigilance. The wide variation between studies excluding or showing an association of the treatment with TNF- α -blockers and the detection of malignant lymphoma might be due to the administration of systemic glucocorticoids in several treatment protocols. Glucocorticoids have a long record of antilymphoproliferative activity and might have curbed development of lymphomas at a very early stage. We should remember that the first trials in which children obtained TNF- α -blockers are just a decade ago and there are no patients with JIA in their forties who received biological DMARDs in their childhood [6]. So, in the absence of long-term safety data, biological DMARDs should be started when conventional treatment with methotrexate and glucocorticoids has failed.
- The strongest argument for the early introduction of TNF- α -blockers rests on the assumption that early and aggressive treatment of RA may prevent definitive damage due to suppression of inflammation and pannus formation and even might hinder the establishment of the false immune reaction leading to chronic inflammatory joint disease. However, in contrast to RA, the pathogenesis of JIA does not progress rapidly to joint destruction with the exception of a few cases of rheumatoid factor positive polyarticular JIA that resembles RA starting already in adolescence. There is no lasting damage in JIA and no loss of a window of opportunity during the period of the slowly starting efficacy of methotrexate especially in the presence of concomitant treatment with systemic glucocorticoids.

We believe it is wrong to withhold systemic glucocorticoids from children with polyarticular JIA. It is correct that the efficacy of the drug should be tested in controlled trials. The lack of the appropriate evidence is the pediatric rheumatology community's fault and this negligence should not lead to our patients' disadvantage. We have to acquire the drug in our modern way by controlled trials. Till these results will be available, we should keep the drug and continue using it based on the therapeutic experience of the last decades.

The authors suggest updating their recommendations which is laudable [3]. However, they should not only focus on areas of newly published evidence, but include available older knowledge on effective treatment of JIA and transform it into new evidence by controlled studies. Moreover, the authors might consider broadening the basis of their recommendations by including the Pediatric Rheumatology European Society. Recent recommendations concerning RA were jointly published by ACR and EULAR.

Further criticisms include:

- Tocilizumab is not mentioned since the authors claim the drug is not widely commercially available. It is licensed for JIA in Japan, for systemic JIA in the US and for RA in Europe and has just been licensed for systemic JIA in Europe.
- Hydroxychloroquine is labeled inappropriate for active synovitis [3]. However, the results of trials are inconclusive and the largest study included patients with severe arthritis and an unexplained improvement in the placebo group [7]. The drug is known to act very slowly and if there are other means including intra-articular steroids to control acute arthritis, it may well prevent flare with a very good safety record.
- Rituximab is recommended as a possible alternative when TNF- α -blocker and abatacept have failed. This is based solely on references concerning RA. There is no pediatric evidence beyond case reports. The drug is known to affect permanently the growing B-cell-compartment in children and there are no data on long-term safety. Rituximab should be reserved for very rare cases or given in controlled trials in JIA only.
- Methotrexate is recommended at 15 mg/m² administered by parenteral route. The drug usually is given at 10–12 mg/m², and there is no convincing evidence in children that the parenteral route is superior to the oral route which might be more appropriate for children. Most of the recent controlled trials for the assessment of new biological DMARDs included as an inclusion criterion failure or toxicity of oral methotrexate at the lower dosage. A PRINTO study demonstrated the efficacy of 15 mg/m² via the parenteral route after 8–12.5 mg/m² orally had failed [8]. However, the study had no control group and continuation of the oral treatment might have been equally effective. Thus, when oral methotrexate fails to control arthritis, a TNF- α -blocker may be considered without having administered parenteral methotrexate.
- Abatacept is a special, although instructive, case: there is a single-controlled trial in polyarticular JIA which showed efficacy and which was followed by FDA and EMA approval [9]. The authors recommend the drug for polyarticular JIA which did not improve on TNF- α -blockers. However, there are no other data confirming the initial publication, and there are no data on long-term safety. It is not enough to show a drug's efficacy in one controlled trial. The drug has to show consistent efficacy over years and a good safety record which can be determined by registries as has been shown for etanercept [10–13]. Such registries are missing for abatacept, tocilizumab and adalimumab. Manufacturers should be forced to continue surveillance of drug safety and efficacy after license under the threat of revoking license if there is lack of compliance.
- The authors use scenarios based on key clinical decision parameters (disease phenotype, prognostic features, disease activity and current therapy). They state that the definitions and values of all these key parameters were “as evidence-based as possible” [3]. However, the process of achieving evidence obviously was based upon expert opinion on “their personal clinical experience” gathered via electronic mail. This discrepancy between the strict adherence to evidence from controlled trials on therapeutic agents on the one hand and the method of defining key parameters of patient stratification on the other hand is remarkable.
- As the authors point out, their recommendations require clear definitions of disease activity including biomarkers to make rational therapeutic choices. While certainly normal levels of C-reactive protein and erythrocyte sedimentation rate are consistent with the definition of low disease activity, there is evidence that these measures are not sensitive enough to exclude local inflammatory activity related to joint destruction. The need for more sophisticated molecular markers indicating disease activity but also prognosis is evident, and first encouraging examples have recently been published in JIA [14].

Our remarks are meant to encourage discussion and not to belittle the tremendous progress for the treatment of JIA which has been achieved by creating these recommendations. The authors have altered the approach to the patient with JIA by creating the JIA treatment groups, by establishing features of poor prognosis and by formulating different levels of disease activity. Use of these features all over the world will show if these new tools will stand up against the necessities of daily care and how they might be modified. However, treating children with JIA will not be the same as before the publication of these recommendations.

Summary

Investigators mainly from North America have established a new classification of juvenile idiopathic arthritis (JIA) by creating treatment groups, levels of disease activity and prognostic features [3]. After scanning the available litera-

ture for controlled trials the authors recommend treatment options. Due to the lack of published evidence these authors could not find an indication for the use of systemic steroids in chronic synovitis. Since this drug may be very useful for patients with JIA and its introduction predates evidence-based medicine, it should not be removed from treatment algorithms, but should be tested in controlled trials. Further topics of discussion relate to treatment with tocilizumab, rituximab, methotrexate, hydroxychloroquine, abatacept and to varying levels of evidence in treatment recommendations. Beukelman et al. will have a lasting impact on the treatment of JIA. European Societies for Pediatric Rheumatology should participate in future developments.

Disclosure Huppertz: HIH served as board member for Abbott, Pfizer, Roche and Swedish Orphan and received speaking fees from Abbott and Pfizer.

Foell: DF served as board member for Roche.

Girschick: no disclosures.

Minden: KM served as board member for Abbott, BMS, Pfizer and Roche and received an unconditional grant from Pfizer.

Horneff: GH served as board member for Abbott, Novartis, Nycomed, Pfizer, Roche and Swedish Orphan, received unconditional grants from Abbott and Pfizer and speaking fees from Abbott, Chugai, Novartis and Pfizer.

References

- Petty RE, Southwood TR, Baum J et al (1998) Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban 1997. *J Rheumatol* 25:1991–1994
- Aletaha D, Neogi T, Silman AJ et al (2010) Rheumatoid arthritis classification criteria. *Arthritis Rheum* 62:2569–2581
- Beukelman T, Patkar NM, Saag KG et al (2011) American college of rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res* 63:465–482
- Dannecker G (2007) Polyarthritis. In: Wagner N, Dannecker G (eds) *Pädiatrische Rheumatologie*. Springer, Heidelberg
- Lovell DJ, Ruperto N, Goodman S et al (2008) Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 359:810–820
- Lovell DJ, Giannini EH, Reiff A et al (2000) Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med* 342:763–769
- Brewer EJ, Giannini EH, Kuzmina N, Alekseev L (1986) Penicillamine and hydroxychloroquine in the treatment of severe juvenile rheumatoid arthritis. Results of the U.S.A.–U.S.S.R. double-blind placebo-controlled trial. *N Engl J Med* 314:1269–1276
- Ruperto N, Murray KJ, Gerloni V, Wulfraat N, de Oliveira SK, Falcini FA et al (2004) A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum* 50:2191–2201
- Ruperto N, Lovell DJ, Quartier P et al (2008) Abatacept in children with juvenile idiopathic arthritis: a randomized, double-blind, placebo-controlled withdrawal trial. *Lancet* 372:383–391
- Horneff G, De Bock F, Foeldvari I et al (2009) German and Austrian Paediatric Rheumatology Collaborative Study Group. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. *Ann Rheum Dis* 68:519–525
- Prince FH, Twilt M, ten Cate R et al (2009) Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. *Ann Rheum Dis* 68:635–641
- Southwood TR, Foster HE, Davidson JE et al (2011) Duration of etanercept treatment and reasons for discontinuation in a cohort of juvenile idiopathic arthritis patients. *Rheumatology (Oxford)* 50:189–195
- Giannini EH, Ilowite NT, Lovell DJ et al (2009) Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. *Arthritis Rheum* 60:2794–2804
- Foell D, Wulfraat N, Wedderburn LR et al (2010) Methotrexate withdrawal at 6 versus 12 months in juvenile idiopathic arthritis in remission: a randomized clinical trial. *JAMA* 303:1266–1273