Perspective

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The future of treatment for juvenile idiopathic arthritis

Juvenile idiopathic arthritis is the most common pediatric rheumatic condition. Advances in identification of cytokines, inflammatory networks and genes involved in the pathogenesis of the disease may lead us towards a more personalized approach to treatment and a biological classification of juvenile idiopathic arthritis. Identification of biomarkers for disease activity, response to treatment and use of ultrasound may improve the definition of inactive disease and remission. New treatment targets and use of comparative effectiveness research can facilitate protocolized treatment that is specific to each child's disease.

Keywords: biomarkers • clinical inactive disease • comparative effectiveness research • juvenile idiopathic arthritis • personalized medicine • pharmacovigilance • remission • treatment • treat to target

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Distinguish how biomarkers may be used in the management of juvenile idiopathic arthritis (JIA)
- Assess different biomarkers for JIA
- Evaluate ultrasound and magnetic resonance imaging as imaging modalities among patients with JIA
- Analyze biologic agents for the treatment of JIA

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Juvenile idiopathic arthritis (JIA) is a chronic inflammatory arthritis that initially presents in children younger than 16 years of age. It is the most commonly occurring pediatric rheumatic illness worldwide [1]. The International League of Associations for Rheumatology classification is currently the most widely used to identify seven distinct categories of JIA, including systemic, oligoarticular (persistent and extended), rheumatoid factor (RF)-negative and -positive polyarticular, psoriatic, enthesitis-related and undifferentiated arthritis [2]. Despite the different categories of JIA, goals of treatment are the same, to completely suppress inflammation with resultant normal growth and physical activity. Treatment of JIA has dramatically changed over the past 15 years with the approval of the first biologic medication to treat JIA in the USA in 1999. Now, with the focus of arthritis treatment moving to a treat-to-target approach, the importance of a clear definition of inactive disease and remission becomes paramount. The use of new tools, such as ultrasound and MRI, may give us an objective measure to refine our current definitions of inactive disease and remission. Additionally, our advances in translational research have made personalized medicine and identification of useful biomarkers an attainable goal. Comparative effectiveness research will aid in the development of new treatments to continue to reduce the morbidity of JIA. New drug developments are also underway that will allow us to target different pathways of inflammation and offer more choices for effective disease modifying antirheumatic drugs (DMARDs).

Personalized medicine & biologic definition of disease

Cytokines, inflammatory networks and genomic studies in children with JIA have revealed insights into pathogenesis and will ultimately enable us to reclassify the categories of JIA biologically in contrast with International League of Associations for Rheumatology definitions or classification based on the number of involved joints and clinical features of disease. Evaluation of peripheral blood mononuclear cells in early-onset JIA, prior to treatment, demonstrates differences in the JIA categories. Persistent oligoarticular JIA was found to be controlled by JAK/STAT, ERK/MAPK, IL-2 and B-cell receptor signaling pathways. However, patients with persistent oligoarticular disease along with RF-negative polyarticular and systemic JIA demonstrated upregulation of IL-10. Finally, in systemic JIA, upregulation of IL-6, TLR/IL-1 receptor and PPAR signaling was also noted [3]. While systemic JIA is clearly phenotypically distinct from oligoarticular disease, some features may overlap with polyarticular disease. Interestingly, systemic JIA appears to have a similar cytokine profile in its synovial fluid to rheumatoid arthritis (RA) synovial fluid [4]. Although it has been shown that IL-1, IL-6 and IL-18 are increased in active systemic JIA, further research suggests that there may be two distinct subsets of patients with systemic JIA. One subset has a predominance of arthritis, IL-6 activation and elevated serum MMP-3, while the other has predominant IL-1 and IL-18 expression with predisposition to development of macrophage activation syndrome [5,6]. In a recent genotype study of 2816 patients with oligoarticular and RF-negative polyarticular JIA, three loci were confirmed to be associated with development of JIA, including HLA region, PTPN22 and PTPN2, with 14 new loci identified [7]. Additionally, through a genome-wide association study of the same JIA categories, chromosome region 3q13 has been identified to promote development of disease [8]. These exciting new advances will help to clarify pathogenesis and, thus, the biologic definition of each JIA category and direct care in the future.

Personalized medicine is currently being used routinely in the field of oncology with incorporation of pharmacogenomic information into the US FDA-labeled indications of several medications to improve efficacy and reduce adverse effects [9,10]. In rheumatology, we are far from this goal, but identifying cytokine profiles in RA has helped to develop a more directed approach to therapy. Recent studies

have shown benefits in using TNF-α inhibitors in RA patients with high baseline TNF levels, as well as using therapeutic drug monitoring to evaluate the efficacy and development of antibodies. However, no single marker can currently predict response to treatment [11]. Furthermore, applying the knowledge from RA studies directly to JIA is not possible given the variability in expression of drug metabolism pathways in childhood [12]. To date, the majority of pharmacogenomic research in JIA has focused on methotrexate, although recent studies on tocilizumab and infliximab have demonstrated the need for higher doses in younger children [12–14]. Given the phenotypic variation in categories of JIA with the additional differences in ontogeny, it has been proposed that instead of attempting to extrapolate data from adult RA studies, the search for pediatric-specific biomarkers should be accomplished with children [15].

Definition of inactive disease & remission

A uniform definition of remission in JIA was not developed until 2004. Through collaboration with experienced pediatric rheumatologists worldwide, preliminary definitions for three stages of quiescent disease were determined. The stages included inactive disease, clinical remission on medication (CRM) and clinical remission off medication (CR). It was felt that remission should be a durable state and have predictive meaning, so time parameters and on and off medications were included in these definitions [16]. The criteria were later validated using data from a large randomized clinical trial in patients with polyarticular-course JIA. The criteria were not able to include biological evidence of inactive disease, so were deemed clinical inactive disease criteria [17]. The ACR and European League Against Rheumatism attempted to form a single definition of remission in RA for use in clinical trials, but ultimately agreed upon two definitions using different approaches [18]. The modifications in the definitions of remission for both RA and JIA underscore the fact that as these definitions are used they will continue to evolve and change [17]. Additionally, as biomarkers for JIA are identified, it is hoped that these will be included in definitions of inactive disease and remission.

Biomarkers

Biomarkers have been sought to monitor disease activity, predict and guide response to treatment, including defining remission. Current potential biomarkers in JIA include erythrocyte sedimentation rate, CRP, antinuclear antibody, RF and CCP antibody [19]. More recently explored biomarkers include MRP8/14 heterocomplex (S100A8/A9; calprotectin), S100A12 and high sensitivity CRP (hs CRP). MRP8/14 has been shown to be elevated in JIA patients with clinically active disease and is a marker for risk of relapse in patients whose clinical examination suggests inactive disease and medications are stopped [20]. S100A12 additionally may be an indicator of synovial inflammation, although clinical arthritis may not be apparent [21]. S100A12 has also been shown to be useful in helping distinguish new onset systemic JIA from other causes of fever of unknown origin, such as infection, malignancy and several periodic fever syndromes [22]. Gerss *et al.* evaluated the utility of using a combination of biomarkers to detect active disease, including S100A12, hs CRP and MRP8/14. The study demonstrated that combining S100A12 and hs CRP may be most precise in predicting flares of patients with inactive JIA. This group also found that the use of the three tests was not more accurate [23]. The possibility of using a combination of biomarkers to predict disease activity in JIA is an emerging area of research. The utility of these newer biomarkers in routine clinical care is promising and can assist in diagnosis of JIA, particularly a diagnosis of systemic JIA, which can be difficult if synovitis is not present at the onset of illness. The identification of biomarkers can also be helpful in managing response to treatment and hopefully for biologically defining remission in JIA.

Prognostic inflammatory networks have been identified by evaluation of peripheral blood mononuclear cells using gene expression profiling in polyarticular JIA patients. They have revealed biologically distinct states representing clinically validated stages of remission. When comparing children with active disease with those in CRM, 23 genes were differentially expressed and a single network of IFN-γ-, IL-6- and IL-4-regulated genes was found. Suppression of this network results in CRM. When comparing patients in CRM versus CR, 39 genes were differentially expressed and represented leukocyte proinflammatory regulators, such as NF-κB and Jun, and IFN-γ and TNF-α. Finally, this group also demonstrated that when comparing normal children with those with JIA in CR, there were 74 upregulated and eight downregulated genes. These findings suggest that CRM and CR are not a return to normal, but likely a state of balance between proinflammatory and anti-inflammatory mechanisms [24]. This is an important area of research and may change how we think about JIA – is it a life long disease? Clearly inflammatory networks, rather than single abnormalities, will need to be incorporated into our concept of a 'biomarker' of disease.

Biomarkers that have recently been developed for RA and are commercially available may prove useful in JIA. Vectra DA, a composite measure of 12

biomarkers also known as multibiomarker disease activity (MBDA) test, has been validated as a biomarker for seronegative and seropositive RA disease activity. MBDA score correlated to a 28 joint count Disease Activity Score using CRP (DAS28-CRP), and changes were noted as early as 2 weeks after treatment initiation [25]. The MBDA test was also confirmed to correlate with DAS28-ESR, ACR/EULAR criteria for remission in RA, Simplified Disease Activity Index, and Clinical Disease Activity Index in the BeSt study, in addition to tracking changes in disease activity over time [26]. MBDA-defined remission has also been shown to correlate with limited progression of radiographic damage in RA as opposed to the DAS28-CRP, which does not. Alternatively, elevated MBDA scores predict progression of radiologic damage [27]. Clinical application in routine practice has been evaluated and demonstrated a change in treatment decision in 38% of cases. These alterations in treatment not only included starting and changing medication or dosage, but also discontinuing medications [28]. No studies have yet reported the usefulness of this biomarker test in JIA, but given the cited benefits in RA, future research in patients with JIA is warranted. If combination biomarkers accurately reflect disease state, then it may be possible to decrease frequency of visits, thus reducing cost of care [26].

Advances in imaging

Although clinical definitions of remission can be useful, they can often miss radiologic evidence of ongoing inflammation [27]. Radiography has long been a mainstay of monitoring consequences of arthritis but until recently we had no standardized scoring system for children with JIA, who have unique features in comparison to RA. As the hip is one of the most frequently affected by arthritis in JIA, the Childhood Arthritis Radiographic Score of the Hip was recently developed and validated [29]. Both MRI and ultrasound have identified synovitis that is not clinically apparent by physical examination in patients with JIA [30–35]. Ultrasound is preferred over MRI because of the ability to scan multiple joints, availability, noninvasiveness, not requiring sedation, cost and ability to follow patients at each outpatient clinic visit to assess for flare or response to treatment [32,33,35–37]. Ultrasound and MRI are both superior to radiography in detecting erosions and do not have radiation exposure, but MRI has been demonstrated to be more sensitive than ultrasound [33,38,39]. MRI has the added benefit of detecting early bone marrow edema, which may signal risk for developing erosive disease [38]. Additionally, MRI is the favored method to detect synovitis in the temporomandibular joints and sacroiliac joints [38,40].

Several studies have promoted the benefits of detecting subclinical arthritis using imaging [30–35]. Malattia *et al.* performed MRI evaluation of the wrist after 1 year of treatment in patients with JIA. In total, 55% of these patients were clinically inactive by physical examination, however, only 10% had an MRI that demonstrated inactive disease [31]. Rebollo-Polo *et al.* discovered similar findings of subclinical arthritis with ultrasound of the wrist and ankle in children with JIA in clinical remission, compared with 100% accordance in MRI results with clinical evaluation of the knee. This result was admittedly controversial given findings from other studies in which there were discrepancies between MRI results and clinical examination of the knee. They also reported possible limitations with their one-view approach to ultrasound examination of the knee (pathologic findings were confirmed in a second plane), as lateral and medial views of the knee may have shown active arthritis [34,36]. Breton *et al.* also found that their results of evaluation of metacarpophalangeal joints by ultrasound in JIA may have differed from others secondary to scanning on the dorsal aspect only, as opposed to dorsal and ventral sides of metacarpophalangeal joints. The differences in results and scanning methods highlight the need for standardization of ultrasound examination in JIA [33]. In addition, these studies suggest that clinical examination of particular joints have a higher probability of missing of synovitis, including hands, feet, ankles and wrists [32,33]. In future revisions of remission criteria, it may be helpful to include ultrasound assessment of those joints that most poorly correlate with physical examination findings.

While ultrasound examination of the joints in JIA may provide additional information to refine the definitions of oligoarticular and extended-oligoarticular JIA, remission and inactive disease, it may also be important for detecting early synovitis, and thus help with properly classifying children with JIA. Newly presenting patients thought to have oligoarticular JIA have been found to have more extensive disease by ultrasound. This information can greatly change the treatment approach. Might the existence of disease in more joints than expected explain the 20% that become polyarticular JIA? Were those children who were diagnosed initially as oligoarticular and then became extended oligoarticular, undertreated polyarticular disease from the start? This can have further implications as children with polyarticular JIA may be treated more aggressively and have more medications readily available for use. Subsequently they may have better outcomes and develop less morbidity of disease [32,35,37,38]. Serial ultrasound examinations at routine clinical visits may be very helpful in this respect.

Janow *et al.* found that 35.7% of joints with subclinical synovitis developed clinically apparent synovitis at follow-up 3–6 months after ultrasound evaluation [35]. Magni-Manzoni *et al.* evaluated clinically inactive JIA patients with baseline ultrasounds and again at 2 years if they remained inactive. They found that the frequency of subclinical synovitis at baseline was comparable between patients who later developed a clinical flare of synovitis and in patients who remained in clinical remission [30]. Further research may help to better elucidate the significance of subclinical synovitis.

Power Doppler use in the ultrasound assessment for active synovitis is an important tool, as it adds value to gray scale abnormalities. However, its use in children can be problematic as children have increased physiologic blood flow in developing joints that may confound interpretation [32,36]. Power Doppler signals have also been found to be greater in some previously affected joints, which were currently inactive, as opposed to those with clinical synovitis [30,36]. As there are no standards for interpretation of power Doppler signal, or gray scale abnormalities, some studies have chosen to disregard grade 1 power Doppler signals as they may represent physiologic blood flow [36]. Future research to define normals in children and set standards for use of ultrasound for evaluation of active synovitis in children with JIA will help strengthen its future use. Although ultrasound has proven to be a new powerful tool in JIA, MRI will continue to be the gold standard for evaluation of difficult to assess joints, such as temporomandibular joints and sacroiliac joints, and in evaluation of potentially early erosive disease.

Treat to target

A treat-to-target approach, also known as a tight control strategy, is one in which there is a limited time period in which to adjust treatment to reach a predefined target outcome [41]. In adult RA the treat-to-target approach has been aimed at preventing long-term dysfunction, and if it has occurred, should aim for maximal function, while balancing harm from treatment [42]. This approach accepts low disease activity as a target outcome, while the goal of treatment in JIA is remission of disease. The TREAT study compared early aggressive monotherapy versus therapy with multiple medications at onset of polyarticular JIA and found higher clinical inactive disease and clinical remission on medication with early aggressive therapy, which was further supported by the ACUTE study [43]. The ACUTE study found modified clinical inactive disease in 68% of polyarticular JIA patients on methotrexate and infliximab at 1 year [44]. There is longer term adult data to support the superior radiographic and functional benefits of treating for remission rather than low disease control; with a more stringent definition of adult RA having better outcomes [45–48]. Additionally, patients with RA treated early in disease (less than 1 year or even earlier) and more aggressively have better longer term outcomes [49–51].

Treatments

New options

The available treatments for JIA have dramatically improved over the past 15 years, beginning with etanercept, the first biologic medication approved to treat JIA in the USA in 1999. In 2013, we had new FDA-labeled indications for medications to treat JIA with tocilizumab approval for treatment of polyarticular JIA and canakinumab approval for treatment of systemic JIA. Several studies are currently underway in JIA patients to prove efficacy, determine dosage and monitor safety for medications already approved for the treatment of RA. We can look forward to the availability of golimumab, certolizumab pegol, subcutaneous tocilizumab and subcutaneous abatacept in the near future to be added to the growing number of DMARDs for use in JIA. The availability of more treatment options that can be given subcutaneously at home versus by intravenous infusion will help lessen the burden of disease on patients with JIA and their families. Having more oral medications available can also be beneficial to increase compliance with therapy as injections can be difficult to tolerate, especially in children.

The newest targets for arthritis treatment are the kinase inhibitors. Currently only one drug is approved for treatment of RA, tofacitinib [52]. Tofacitinib, also known as CP-690550, inhibits mainly JAK1 and 3, resulting in inhibition of multiple cytokines including IL-2, -4, -6, -7, -9 and -15 [53,54]. Tofacitinib is an oral medication that has shown clinical response as early as 2 weeks with sustained response up to 12 months. Adverse effects noted in clinical studies included dose-dependent increases in low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, and cytopenias, including anemia and neutropenia [52–55]. The development of new oral DMARDs is exciting and we hope to begin evaluating their use in children with JIA in the near future, starting with tofacitinib. Selective JAK inhibitors are also currently being evaluated that may have a more favorable adverse effect profile [52]. Syk inhibition has been another target in RA treatment. The most notable drug being studied is fostamatinib (R788), an oral medication currently undergoing Phase III study for treatment of RA [52,56,57]. Results from the Phase II study showed clinical response as early as week 1, but there were significant concerns regarding adverse effects. It remains to be seen if fostamatinib can gain

FDA approval for treatment of RA, given the concerns regarding adverse effects, or if newer Syk inhibitors will prove to be superior.

Several other orally bioavailable therapeutic targets that are on the horizon include inhibition of BTK, PI3K and PDE4. BTK inhibition results in reduction of TNF, IL-1 and IL-6 [58], and a Phase I trial of HM71224 is poised to start soon as the first trial in humans using a BTK inhibitor [59]. PI3Ks are divided into three classes, but currently only inhibition of class I is undergoing evaluation in humans. Selective inhibitors of class I PI3K p110 isoforms are being studied for use in RA, as nonselective class I PI3K inhibitors in oncology studies have shown potential toxicity. PDE4 has specificity for cAMP with greater than 20 isoforms expressed throughout the body [58]. Apremilast, an oral PDE4 inhibitor, is undergoing evaluation for treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, among several other inflammatory conditions [58,60–62]. New intravenous therapies are also undergoing evaluation for efficacy in treatment of RA. Ocrelizumab, also known as SBI-087, is an intravenous humanized anti-CD20 that has shown benefit in the treatment of rheumatoid arthritis and halting radiographic progression, but higher doses have demonstrated concerns with safety [63]. Studies continue to be performed with ocrelizumab to determine the ideal dose, timing of use with other DMARDs and safety [64].

Pharmacovigilance

Given the growing number of therapeutic options available to treat JIA, coupled with little knowledge about potential long-term side effects of medications used to treat JIA, pharmacovigilance has become critically important in pediatric rheumatology. Standard prior approaches to gather drug safety information have been fraught with limitations, including small numbers of patients from open-label, long-term extension studies of new medications, passive adverse event surveillance reporting by physicians and limited product-specific industry-sponsored registries [65]. The Childhood Arthritis and Rheumatology Research Alliance-Consolidated Safety Registry (CARRA-CoRe), now termed the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, in the USA and Pharmachild in the EU are examples of broad-based long-term pharmacovigilance approaches that aim to capture exposure to a wide array of treatments, including new medications, and standardize collection of serious adverse and important medical events. These large registries may be able to fulfill postmarketing surveillance requirements [65,66] in North America and Europe.

Comparative effectiveness research

Given the growing number of medications to treat JIA, comparative effectiveness research is vital to help determine which combinations or escalation of medical therapy may be most beneficial for each JIA category to obtain the best outcome. This research can provide valuable information regarding real-world care and management of JIA using medications that have already been proven to be effective, but can help to identify specific biologic and clinical characteristics that may respond differently with each treatment [67]. Using data from a large database of well-characterized patients in terms of disease characteristics, treatments and response has allowed for the standardization of treatment protocols, which has been shown to improve outcomes in other medical fields, such as in the treatment of childhood malignancies [68].

CARRA has undertaken an effort to develop consensus treatment plans for multiple pediatric autoimmune diseases, including the systemic and polyarticular JIA categories [68,69]. These plans were developed with guidance and expertise from the membership of CARRA, which includes the majority of practicing pediatric rheumatologists in North America. Currently, published consensus treatment plans exist for care of children with systemic JIA and data is being collected on these treatment plans via The CARRA Registry, a North American registry of children with rheumatic diseases. These plans standardize data collection and outcome measures at routine intervals for four treatment options during the initial 9 months of treatment after diagnosis of systemic JIA [68]. We anticipate that this research will provide evidence-based guidance on the best care for an individual with systemic JIA. Consensus treatment plans are being developed for other JIA categories, including polyarticular JIA and enthesitis-related arthritis [69]. We hope that by developing standardized treatment plans, we can move toward protocolized treatment that is specific to each child's disease.

Conclusion

With the advances in translational research, the pathogenesis of JIA is becoming more apparent. As we continue to identify the key cytokines, inflammatory networks and genomic underpinnings for JIA, we hope to have categories of JIA based on biology, rather than phenotype, leading to personalized treatments that can be more accurately directed and more effective with the hope that potential cures may be found. Using new tools in imaging and with identification of biomarkers, we can properly identify remission biologically as well as clinically. A biologic definition of remission can provide a higher target goal in treatment, which,

combined with evidence-based comparative effectiveness studies and pharmacovigilance, will facilitate identifying the best treatment at the best time for each child with JIA.

Future perspective

In the future, JIA will be biologically classified, instead of phenotypically classified. Treatment will target specific cytokine and inflammatory networks for a personalized approach to therapy. Biomarkers will be routinely used to identify treatment approach, as well as to predict response to treatment. A biologic definition of inactive disease and remission will be available to more accurately determine these stages. Protocolized treatment will be used based on each child's biologic disease profile.

Executive Summary

Personalized medicine & biologic definition of disease

- New advances in identification of cytokines and genes involved in juvenile idiopathic arthritis (JIA) will help to redefine JIA categories and direct care with a more personalized approach.

Definition of inactive disease & remission

- Biomarkers will help us to add a definition of biologic inactive disease to the current clinical remission criteria, which can be used as a target for clinical trials, comparative effectiveness studies and clinical care.
- Ultrasound use in routine clinical care can be helpful in identifying subclinical synovitis, but standard protocols and definitions need to be determined before incorporating its use in helping to define inactive disease.

Treat to target

- To find the optimal target for treatment of JIA we must standardize our definition of remission and disease activity.

Treatments

- There are a growing number of available medications to treat JIA, with more available methods of administration and new targets, including the kinase inhibitors.
- New pharmacovigilance efforts will more effectively capture adverse events for multiple medications using large long-term registries.
- Comparative effectiveness research will help us to make more effective choices in treatment based on each child's disease characteristics.

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The future of treatment for juvenile idiopathic arthritis

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. You are asked to see a 7-year-old girl who was recently diagnosed with systemic juvenile idiopathic arthritis (JIA). What should you consider regarding this diagnosis?

- ☐ **A** The synovial cytokine profile is highly different in comparing systemic JIA vs rheumatoid arthritis
- ☐ **B** Interleukin (IL)-1 and IL-18 expression are associated with an increased risk for macrophage activation syndrome
- ☐ **C** Serum levels of tumor necrosis factor (TNF) do not predict treatment response to TNF inhibitors
- ☐ **D** Serum levels of IL-1 accurately predict response to treatment

2. Which of the following statements regarding specific biomarkers in JIA is ***most*** accurate?

- ☐ **A** Higher levels of myeloid-related protein 8 and 14 heterocomplex (MRP8/14) are associated with reduced disease activity
- ☐ **B** S100A12 cannot differentiate JIA from other causes of fever of unknown origin
- ☐ **C** The combination of S100A12, high-sensitivity C-reactive protein, and MRP8/14 is the best method to predict flares of JIA
- ☐ **D** Multibiomarker disease activity scores can predict the degree of radiologic damage to joints

3.	You order a radiologic evaluation for this patient. What should you consider when ordering this testing?	
☐	**A**	Ultrasound examination can identify synovitis that is not clinically active
☐	**B**	Magnetic resonance imaging is similar to ultrasound in its sensitivity to detect erosions
☐	**C**	Nearly all joints with subclinical synovitis on ultrasound examination demonstrate clinical synovitis within 6 months
☐	**D**	Power Doppler ultrasound testing is more facile to use among children vs adults

4.	Which of the statements regarding the study and practice of treatments of JIA is ***most*** accurate?	
☐	**A**	Tofacitinib has not been demonstrated to be effective beyond 6 weeks of treatment
☐	**B**	Tofacitinib is associated with increases in serum lipid levels, anemia, and neutropenia
☐	**C**	Safety is the principal advantage of treatment with fostamatinib
☐	**D**	Comparative effectiveness research for new biologic treatments is largely unnecessary