Safety of TNF inhibitors in adolescents and children

Lauren Keyser McCluggage
Clinical Pharmacy, Philadelphia College of Pharmacy, Philadelphia, PA, USA

Abstract: This article describes the use of tumor necrosis factor (TNF) inhibitors in children, reviews the pharmacology of these agents, and reviews and summarizes the current safety information available for etanercept, adalimumab, and infliximab. TNF inhibitors are being used for a variety of indications in children including Crohn’s disease and juvenile idiopathic arthritis. However, the full safety profile of these agents is still not known. In adult patients, TNF inhibitors have demonstrated a variety of adverse effects including increased risk of infection, malignancy, demyelinating disorders, and reactivation of latent diseases. In children the rate of adverse effects is harder to elucidate due to the limited number of patients in clinical trials and limited case reports. However, based on the data available, TNF inhibitors have been implicated in increasing the rate of malignancy in children, especially the rate of lymphoma. In addition, similarly with adults the rate of infections is increased and the types of infections are more rare or opportunistic. One of the more common adverse effects continues to be infusion or injection-site reactions, although children tend to have a lower rate of infusion reactions with infliximab compared to adults. Based on the limited safety information and long-term effect data, TNF inhibitors should be reserved in children for patients with refractory disease and the risks need to be understood and assessed prior to initiation.

Keywords: TNF-alpha inhibitors, adverse effects, safety, children

Introduction
Tumor necrosis factor (TNF) inhibitors have been used for many autoimmune diseases in both children and adults. These agents have been shown to be efficacious for rheumatoid arthritis, Crohn’s disease, ankylosing spondylitis, juvenile idiopathic arthritis (JIA), and psoriatic arthritis and are continually being researched for roles in other disease processes.1–5 However, with all medications the risks and benefits must be assessed and balanced.

The TNF inhibitors have been associated with various adverse effects including infections and malignancies. The risk for infection can range from mild infection to reactivation of latent infections such as tuberculosis or hepatitis. In addition, there are less data available on how TNF inhibitors affect children and the risks they pose to this subpopulation. Therefore, the objective of this article is to review the use of TNF inhibitors in children and provide a detailed analysis of the safety information available for these agents, focusing on the agents the US Food and Drug Administration (FDA) has approved for children.
TNF inhibitor pharmacology

TNF-alpha exerts a variety of functions within the body. At low concentrations, TNF-alpha induces the body’s immune response to local injury or infection. However, in states of overproduction TNF-alpha leads to increased inflammation and possible organ injury. TNF-alpha is overproduced in multiple autoimmune conditions including rheumatoid arthritis, Crohn’s disease, psoriasis, psoriatic arthritis, and ankylosing spondylitis.6

TNF-alpha is produced from various cells including macrophages, T-cells, mast cells, granulocytes, and fibroblasts. Once released, TNF-alpha exerts many effects depending on the location and underlying medical condition. For example, in patients with rheumatoid arthritis, TNF-alpha initiates matrix degradation and stimulates osteoclast activity, whereas in patients with Crohn’s disease, TNF-alpha activity results in granuloma formation. Regardless of the underlying condition, TNF-alpha induces inflammation by stimulation of pro-inflammatory cytokines and is an important component in both innate and adaptive immunity.5

Although all of the current TNF inhibitors result in decreasing concentrations of TNF-alpha, there are many differences between them. Infliximab, adalimumab, and golimumab are monoclonal antibodies specific to TNF.1,4–6 However, infliximab is a chimeric mouse–human monoclonal antibody which is only 70% to 75% humanized whereas adalimumab and golimumab are 100% humanized.6,7 In contrast, etanercept is a dimer of 2 human TNF receptors bound to the Fc portion of a human monoclonal antibody.1,6 Certolizumab pegol is a humanized antibody Fab fragment and is conjugated to polyethylene glycol.2,6

These structural differences result in minor differences in their effects. Infliximab, adalimumab, golimumab, and certolizumab pegol are able to bind both soluble and transmembrane bound TNF-alpha. Etanercept can only bind to soluble TNF-alpha but is able to also bind to TNF-beta which the others cannot. Also, infliximab, adalimumab, and golimumab can induce apoptosis of cells that produce TNF-alpha, but etanercept and certolizumab pegol cannot. Although these differences have been elucidated, the full impact on clinical outcomes has yet to be determined.6

The variations among the TNF inhibitors become more apparent when assessing the dosing regimens of the various agents. All except infliximab, which is an intravenous infusion, are given as a subcutaneous injection but with varying intervals ranging from biweekly to monthly. Table 1 outlines some of the key similarities and differences in the pharmacology of the TNF inhibitors.

Clinical efficacy in children

Of the 5 available TNF inhibitors, only infliximab, adalimumab, and etanercept have FDA-approved indications for children. Infliximab is approved to treat moderately to severely active Crohn’s disease in children greater than 6 years old who have not responded adequately to conventional therapy.5 Adalimumab is approved to treat moderately

### Table 1 Summary of select pharmacologic properties of tumor necrosis factor-alpha inhibitors

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Adalimumab</th>
<th>Cetolizumab</th>
<th>Etanercept</th>
<th>Golimumab</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved adult indications</td>
<td>Rheumatoid arthritis</td>
<td>Psoriatic arthritis</td>
<td>Crohn’s disease</td>
<td>Rheumatoid arthritis</td>
<td>Psoriatic arthritis</td>
</tr>
<tr>
<td></td>
<td>Psoriatic arthritis</td>
<td>Rheumatoid arthritis</td>
<td>Plaque psoriasis</td>
<td>Plaque psoriasis</td>
<td>Plaque psoriasis</td>
</tr>
<tr>
<td>FDA indication for children</td>
<td>≥4 years old for polyarticular juvenile idiopathic arthritis</td>
<td>≥2 years old for polyarticular juvenile idiopathic arthritis</td>
<td>None</td>
<td>None</td>
<td>≥6 years old for Crohn’s disease</td>
</tr>
<tr>
<td>Dosage for children based on FDA approval</td>
<td>&lt;15 kg: not recommended</td>
<td>0.4 mg/kg subcutaneously twice weekly or 0.8 mg/kg subcutaneously weekly (max of 50 mg per week)</td>
<td>5 mg/kg IV weeks 0, 2, and 6 then every 8 weeks thereafter</td>
<td>100% humanized monoclonal antibody</td>
<td>100% humanized monoclonal antibody</td>
</tr>
<tr>
<td></td>
<td>15 to &lt;30 kg: 20 mg every other week</td>
<td></td>
<td></td>
<td>Fc portion of 100% humanized monoclonal antibody fragment</td>
<td>72–132 hours</td>
</tr>
<tr>
<td></td>
<td>≥30 kg: 40 mg every other week</td>
<td></td>
<td></td>
<td>100% humanized monoclonal antibody</td>
<td>14 days</td>
</tr>
<tr>
<td>Class</td>
<td>100% humanized monoclonal antibody</td>
<td>100% humanized monoclonal antibody fragment</td>
<td></td>
<td>100% humanized monoclonal antibody</td>
<td>Chimeric monoclonal antibody</td>
</tr>
<tr>
<td>Half-life</td>
<td>10–20 days</td>
<td>14 days</td>
<td></td>
<td>14 days</td>
<td>7–12 days</td>
</tr>
</tbody>
</table>
to severely active polyarticular JIA in children 4 years of age or older and etanercept is approved for moderately to severely active polyarticular JIA in children 2 years of age or older.\(^5\) Golimumab and certolizumab have not been shown to be ineffective in children, there are just not any data currently to support their use in children. Therefore, this article will detail the information available for the pediatric-approved medications.

Infliximab was studied in pediatric patients with Crohn’s disease as induction therapy and maintenance therapy. After induction therapy (infusions at weeks 0, 2, and 6), 88% of patients had a clinical response and 59% were in clinical remission. After 1 year of maintenance therapy, infliximab every 8 weeks, 56% of patients were in clinical remission.\(^5\)

The landmark study evaluating the effect of etanercept for JIA was conducted in 69 children aged 4 to 17 years old with active polyarticular JIA. All patients had to have been treated with methotrexate with an inadequate response. There were 2 portions to the trial: open label treatment for 3 months; and double blind randomized treatment for months 4 to 7. In the open label portion of the trial, 74% of patients treated with etanercept experienced a clinical response defined as ≥30% improvement in 3 of the 6 components (active joint count, number of joints with limitation of motion, physician and patient/parent global assessments, functional assessment, and erythrocyte sedimentation rate). In addition, 64% experienced a 50% improvement and 36% experienced a 70% improvement. For the double blind portion, only 24% of patients treated with etanercept experienced a disease flare compared to 77% of patients treated with placebo (\(P = 0.003\)).\(^8\) In an extension analysis of these patients, etanercept response was durable over 8 years of treatment.\(^9\)

Adalimumab was assessed in a similar manner as etanercept in pediatric patients with JIA. One hundred seventy-one patients with active JIA who either were naïve to methotrexate or previously treated with methotrexate were assessed. During the open label portion of the trial, 84% of patients treated with adalimumab experienced a response (defined the same as in the etanercept trial). In the double blind portion of the trial, patients treated with adalimumab had a lower rate of disease flare (40%) compared to patients treated with placebo (68%). Also of importance is the fact that the patient’s or parent’s assessment of pain decreased by 48% to 60% when adalimumab therapy was initiated. The benefits of adalimumab were similar regardless of previous methotrexate use.\(^10\)

As is apparent from these data, the TNF inhibitors are potent, effective agents that can induce remission and response in patients either naïve or intolerant to more traditional therapies. However whenever assessing medications’ benefits, the risks also need to be assessed.

### Safety and tolerability

As mentioned prior, multiple safety issues exist about the use of TNF inhibitors. The FDA has mandated box warnings for these agents on the increased risk of infections and possible increased risk of malignancies.

### Malignancies

Data suggest that TNF inhibitors may increase the risk of malignancy, especially lymphomas. Although the exact mechanism for this is unknown, it is thought to be due to decreased immune function and immunologic surveillance caused by immunosuppressants. To address this concern, in August 2009 the FDA completed an analysis investigating the risk of malignancies associated with TNF inhibitors. Forty-eight cases of malignancies were identified in children using TNF inhibitors. The majority of these cases were lymphomas but other malignancies such as leukemia, melanoma, renal cell carcinoma, and other solid organ malignancies were observed.\(^11\)

An in-depth review of these cases was published which provided more details.\(^12\) Of the 48 cases, 31 of the patients were taking infliximab, 15 were taking etanercept, and 2 were taking adalimumab. The 2 patients taking adalimumab had both been previously treated with infliximab which makes causation harder to prove. Over 85% of patients were on concomitant immunosuppressants. One-half of patients were being treated for inflammatory bowel disease and approximately one-third of the patients were taking a TNF inhibitor for JIA. The rate of reporting of malignancy for patients receiving infliximab was 4 times greater than the background rate of reporting for the general pediatric population. For lymphomas associated with infliximab, the rate of reporting was approximately 18 times that of the background rate. For etanercept, the overall rate of reporting for malignancies was similar to the background rate. However, the rate of lymphoma reporting was 5 times higher than the background rate.\(^12\) Table 2 provides a further differentiation of the types of malignancies reported.

Another analysis was conducted by the manufacturer of etanercept to investigate the effect of etanercept on malignancies. The analysis included data from 11 years (1998–2009) and patients who received etanercept prior to 18 years of age and developed a malignancy prior to 22 years of age. Based on the data from the randomized controlled
Table 2 Types of malignancies reported to FDA associated with tumor necrosis factor-alpha inhibitors

<table>
<thead>
<tr>
<th>Type of Malignancy</th>
<th>Overall</th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatosplenic T cell lymphoma</td>
<td>10</td>
<td>9</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hodgkin's lymphoma</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B-cell lymphoma</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Leukemia</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>18</td>
<td>11</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>31</td>
<td>15</td>
<td>2</td>
</tr>
</tbody>
</table>

Infections

In the trial that examined the effect of etanercept on JIA, the infection rate was compared to that of adults. In trials including adult patients, the rate of infection was 4% to 8% and the infection rate of pediatric patients was 3.9% with similar types of infections as adults. In one of the analyses reviewed, the rate of herpes zoster in pediatric patients was 3.7%.14

Infliximab: clinical trials

In a review of trials examining infliximab for inflammatory bowel disease in adolescents, the infection rate was compared to that of adults. In trials including adult patients, the rate of infection was 4% to 8% and the infection rate of pediatric patients was 3.9% with similar types of infections as adults. In one of the analyses reviewed, the rate of herpes zoster in pediatric patients was 3.7%.14

These data are in stark contrast to the percentages from the manufacturer. The package insert states that 56% of pediatric patients who received infliximab reported an infection compared to 50% of adults. This discrepancy may be due to the difference in definitions of infections and classification of minor or severe. The majority of infections listed from the manufacturer were upper respiratory tract infections and pharyngitis. Only 6.8% of patients experienced a serious infection, abscess being the most common. Also, there was a difference in infection rate based on dosing interval. Pediatric patients receiving infliximab every 8 weeks had a much higher rate of infections (74%) than patients receiving it every 12 weeks (38%).5

Etanercept: clinical trials

In the trial that examined the effect of etanercept on JIA, the rate of upper respiratory tract infections was 35% during the open labeled portion. In the 2-year extension of the trial, 15% of patients had to be hospitalized for a serious adverse event, most of which were infectious etiologies.5 After the
4-year extension portion, the rate of serious infections was determined to be 0.04 per patient-year.1 In safety data from the 8-year extension trial, there was no increase in the rate of serious adverse events.7

Safety of etanercept was evaluated based on data from a registry of pediatric patients treated with etanercept for JIA. This registry examined the safety of etanercept, methotrexate, or the combination of methotrexate and etanercept. For etanercept monotherapy, the rate of medically important infections was 1.8 per 100 patient-years. This is more than was seen in the methotrexate monotherapy group (1.3 per 100 patient-years), but less than in the combination group (2.1 per 100 patient-years). This validates the theory that the risk of infection increases when patients are on multiple immunosuppressants.15

In a similar German registry, 322 patients treated with etanercept were evaluated representing 592 patient-years. There were reported infections in 20 of these patients. A variety of infections was observed, including bronchitis, herpex simplex labialis, varicella zoster virus infection, cellulitis, and pneumonia. This represents a 6.2% risk of infection with treatment.16

**Adalimumab: clinical trials**

Adalimumab data describe similar infection rates as the other aforementioned TNF inhibitors. In a trial examining the effect of adalimumab on pediatric patients with JIA, the rate for all infections was 45% within the first 16 weeks of therapy whereas the rate for serious infection was 4% within 2 years of initiation of therapy. The serious infections included herpes simplex, pneumonia, and herpes zoster.10

**Case reports**

Since the use of TNF inhibitors has expanded in the pediatric population, many case reports have described infections associated with their use. A case series published in 2010 describes 4 cases of children developing musculoskeletal infections after receiving TNF inhibitors.17 All 4 patients were being treated for JIA and each was on TNF inhibitor plus methotrexate. Two patients were treated with etanercept and the other 2 were treated with infliximab with a total range of TNF inhibitor treatment of 6 to 14 months. In all 4 cases, the patients were found to have a musculoskeletal infection with no inciting event. At this medical center in Vancouver, Canada, 31 children were being treated with TNF inhibitors and these cases represent an adverse effect rate of 12.9%.17

In another case report, a patient being treated with infliximab for Crohn’s disease developed disseminated cytomegalovirus (CMV) infection. The authors described how the presenting symptoms mimic that of a Crohn’s disease flare, making CMV hard to diagnose. Unfortunately in this situation, the disseminated CMV did not respond to antivirals and the infection led to mortality.18

Disseminated cutaneous varicella zoster virus infections are described in 2 patients being treated with infliximab for Crohn’s disease. Both patients had been treated with infliximab for 2 or more years and were also receiving concomitant immunosuppressant therapy (methotrexate and 6-mercaptopurine). In the first case, the child had received the varicella vaccination and was later exposed to a classmate with varicella infection. Her rash covered most of her lower and upper extremities and she was treated successfully with antiviral therapy. The child in the second case had a history of varicella zoster virus infection 13 years prior and received the varicella vaccination. His rash involved his scalp, face, trunk, and extremities. He too was treated successfully with antivirals but had 2 recurrences. The authors cite infliximab as the likely contributing factor since in both cases their Crohn’s disease was well controlled and they had been on long-term infliximab therapy. This case report emphasizes the need for more data on the risk of varicella and other infections in children and determining the best way to diagnose and treat these patients.19

A case report of an 8-year-old boy highlights the risk of opportunistic infections in patients treated with TNF inhibitors. This child’s Crohn’s disease was being treated with infliximab every 5 to 6 weeks for 15 months prior to him developing fevers, cough, anorexia, and night sweats. He was initially treated with a course of azithromycin with some improvement but then subsequent return of symptoms. Once admitted to the hospital, further evaluation was done and cultures of biopsied lymph node revealed *Pneumocystis jiroveci* and *Histoplasma capsulatum*. After treatment for both infections, the child improved but his histoplasmosis antigen remained elevated.20

All of these case reports emphasize the need to consider rarer infectious causes when TNF inhibitor-treated patients present with infectious symptoms. Particular importance should be paid to opportunistic infections and the risk of developing these. In many of these cases, optimal treatment was delayed because these rarer infections were not considered until other therapy failed. Practitioners should consider the potential for these infections when choosing empiric therapy.

**Injection-related reactions**

One of the more common adverse effects of TNF inhibitors is injection- or infusion-related reactions. These can range...
from erythema at the injection site to anaphylaxis reactions associated with infusion. The more serious reactions are associated with infliximab since it is not 100% humanized like the other TNF inhibitors.

When compiling data from 11 evaluations of infliximab use in pediatric patients with inflammatory bowel disease, infusion reactions were observed in 3% to 39% of patients or in 0.8% to 8.6% of infusions. There appears to be a difference in the rate of reactions in pediatric patients and adult patients when re-treated with episodic doses of infliximab. Children less than 17 years old tend to have less infusion reactions than adults. The infusion reactions associated with infliximab can include hypotension, flushing, fever, nausea, tachycardia, pruritis, fatigue, and chest tightness. Premedication does not appear to be beneficial in preventing these infusion reactions but can be useful for decreasing the chance of another reaction with subsequent infusions.14

Reactions associated with etanercept and adalimumab are milder since they do not contain a chimeric portion. In the open label portion of the etanercept study, 39% of patients experienced an injection-site reaction.8 However, in the double blind portion of the study, there was no difference between etanercept and placebo in the rate of injection-site reactions with only 1 patient in each group experiencing a reaction. One possible reason for this is that the reaction is likely a T-lymphocyte mediated delayed-type hypersensitivity. With this type of reaction, tolerance develops with time and the frequency decreases.21 If the reaction needs treatment, cold compresses can be applied or topical antihistamine or corticosteroids can be used. In patients treated with adalimumab, 19% experienced injection-site pain and 16% experienced an injection-site reaction. In addition, 6% of patients had a hypersensitivity reaction to adalimumab that was described as a nonserious, localized, allergic rash.1

**Immunogenicity**

All of the TNF inhibitors have been associated with development of antibodies to the medication. Although these have been measured, the clinical impact is not completely known. For infliximab these antibodies have been associated with increased infusion reactions and loss of effect but for etanercept and adalimumab the clinical impact is not as apparent.

**Infliximab**

Human antichimeric antibody (HACA) production is likely the cause of infusion reactions associated with infliximab. A retrospective analysis was done by Miele et al to determine the rate of HACA production in children treated with infliximab. Of the 132 patients treated with infliximab, only 56 had HACA assays measured and of those 22 were inconclusive due to circulated infliximab in the blood. Of the 34 patient samples remaining, 35% had HACA detected. For the patients who were HACA positive, infusion reactions occurred in a higher proportion of infusions than in patients who were HACA negative (13.8% vs 3.6%, respectively, \( P < 0.01 \)). When assessing the degree of HACA production, patients whose concentrations were 8.0 \( \mu \)g/mL or higher were more likely to experience an infusion reaction. This higher concentration of HACA tended to occur in patients whose infliximab infusions were 8 weeks or less apart. Patients who were on concomitant immunosuppressant therapy had a lower risk of HACA development (relative risk: 0.34, \( P = 0.02 \)) and if HACA developed the concentrations were lower in these patients than in patients not on concomitant therapy. Unfortunately, this analysis did not correlate HACA formation to clinical response.22

Another analysis confirmed the incidence rate of the Miele et al analysis. In this review, of the 22 children treated with infliximab, 35.7% developed HACA. In patients who received induction therapy with only 1 dose, 77.7% developed HACA compared to only 15.7% in patients who received 3 induction doses at weeks 0, 2, and 6 (\( P = 0.0028 \)). The clinical response based on HACA production was assessed in this analysis. Of the 8 children who no longer responded to infliximab therapy, 75% had positive HACA. This is in contrast to the 14 patients who maintained response in which only 21.4% were HACA positive.23

**Etanercept and adalimumab**

In the approval trial for etanercept, only 2 patients of the 25 treated with etanercept developed etanercept antibodies (8%) and these antibodies were considered non-neutralizing.8 No data on the development of these antibodies were reported in the 8-year open label follow-up study.9

Adalimumab antibodies were detected in 27 of the 171 patients (16%) treated in the approval trial. When comparing patients on concomitant methotrexate or not, the rate for patients on methotrexate was 6% compared to 26% for those not receiving methotrexate.10

The clinical response rate was not correlated to the antibody production in either study but the percentages were lower than for infliximab probably due to the lack of a chimeric portion. Based on data from these studies and adult trials, the development of antibodies is a concern particularly for infliximab. Concomitant use with another
the autoantibody production did not affect the patients’ JIA resulting in Hashimoto’s thyroiditis. Although measured, anti-R1 antibodies, and 1 developed anti-thyroid antibodies imab, 5/14 patients on etanercept). Of the 5 patients treated elevated autoantibodies was 23% (1/12 patients on inflixcept for at least 2 years. Overall, the incidence of developing other adverse effects in varying degrees. One of the other serious adverse effects is the increased risk of new onset or exacerbation of demyelinating disorders. To date, there have only been 2 cases reported in patients who had JIA. However, in both cases the patient was 21 years of age at the onset of symptoms.21 However, patients with history of these disorders or seizures should not use TNF inhibitors and if a patient on these therapies presents with mental status changes, demyelinating disorders should be on the differential.

Similarly to other immunosuppressants, the TNF inhibitors may cause pancytopenia, leukopenia, neutropenia, aplastic anemia, or thrombocytopenia. Therefore, the blood counts of patients should be monitored while on therapy and therapy should be discontinued if these effects are noted.

Lastly, TNF inhibitors have been associated with reactivation of hepatitis B virus in patients who are chronic carriers of hepatitis B. Although this is a concern, it is less so for children since the majority of children now receive the hepatitis B vaccination starting at birth. However, if a patient has not received the vaccination and has risk factors for hepatitis B infection, they should be screened prior to initiating therapy.

Place in therapy

The TNF inhibitors offer a treatment option for patients failing treatment with the nonbiologic agents such as methotrexate or azathioprine. In the majority of cases, initiation of TNF inhibitors is associated with a positive clinical response. However due to the limitations of these agents as outlined above, they should not be used as first-line treatment especially in children. New information continues to become available about this class of medications, and with the lack of information in children, the more conservative approach is to reserve the use of these agents for patients with more severe, unresponsive disease.

Because etanercept and adalimumab have the most data supporting their use in pediatric patients, these agents would be preferred over infliximab at this time. Infliximab has the most data to support its use in children with inflammatory bowel disease, whereas, etanercept and adalimumab are indicated for children with JIA. Regardless of the indication of etanercept and initiation of infliximab, all patients experienced a complete remission.23 Although there are only limited data on this adverse effect, it is one that should be investigated further.

Other adverse effects

The TNF inhibitors have been associated with a variety of other adverse effects in varying degrees. One of the other serious adverse effects is the increased risk of new onset or exacerbation of demyelinating disorders. To date, there have only been 2 cases reported in patients who had JIA. However, in both cases the patient was 21 years of age at the onset of symptoms.21 However, patients with history of these disorders or seizures should not use TNF inhibitors and if a patient on these therapies presents with mental status changes, demyelinating disorders should be on the differential.

Similarly to other immunosuppressants, the TNF inhibitors may cause pancytopenia, leukopenia, neutropenia, aplastic anemia, or thrombocytopenia. Therefore, the blood counts of patients should be monitored while on therapy and therapy should be discontinued if these effects are noted.

Lastly, TNF inhibitors have been associated with reactivation of hepatitis B virus in patients who are chronic carriers of hepatitis B. Although this is a concern, it is less so for children since the majority of children now receive the hepatitis B vaccination starting at birth. However, if a patient has not received the vaccination and has risk factors for hepatitis B infection, they should be screened prior to initiating therapy.
or age of the patient, the practitioner and patient need to be aware of the risks associated with these medications and make an informed decision, weighing the risks and benefits.

**Disclosure**
The author declares no conflicts of interest.

**References**