REVIEW

Infliximab: A Review of its use in the Treatment of Pediatric Crohn’s Disease

Arkady Broder¹ and Joel R. Rosh²

¹Department of Medicine, Beth Israel Medical Center, Albert Einstein College of Medicine New York, NY. ²Associate Professor of Pediatrics, UMD—New Jersey Medical School Director, Pediatric Gastroenterology Goryeb Children’s Hospital/Atlantic Health, 100 Madison Avenue, Morristown, NJ 07962. Email: joel.rosh@atlantichealth.org

Abstract: The past decade has brought great change to the treatment of pediatric Crohn’s disease. The majority of affected patients now receive therapy directed at the underlying immune dysregulation that is associated with this chronic disease. The monoclonal antibodies directed against tumor necrosis factor alpha play an increasing role in such therapy. Infliximab is the prototype of this class of biologic based therapy. This review covers the basic pharmacokinetics of infliximab while reviewing the data on its efficacy in pediatric Crohn’s disease patients. Current issues related to infliximab dosing and safety are also reviewed.

Keywords: pediatric, Crohn’s disease, infliximab, therapy

Clinical Medicine Insights: Therapeutics 2010:2 235–243

This article is available from http://www.la-press.com.

© the author(s), publisher and licensee Libertas Academica Ltd.

This is an open access article. Unrestricted non-commercial use is permitted provided the original work is properly cited.

The authors grant exclusive rights to all commercial reproduction and distribution to Libertas Academica. Commercial reproduction and distribution rights are reserved by Libertas Academica. No unauthorised commercial use permitted without express consent of Libertas Academica. Contact tom.hill@la-press.com for further information.
Introduction
The inflammatory bowel diseases (IBD) include Crohn’s disease (CD) and ulcerative colitis (UC). These conditions have genetic underpinnings and are associated with dysregulation of innate and adaptive immunity having impact upon gastrointestinal and extra-intestinal sites. Since its original description in 1932, the incidence of Crohn’s disease (CD) in the developed world continues to rise. This is true of pediatric CD as well with a reported yearly incidence as high as 4.5 per 100,000. Approximately 25% of Crohn’s disease patients are diagnosed during childhood and IBD has become one of the most common chronic inflammatory conditions in this population.

Recent studies have documented childhood-onset CD to be a more aggressive clinical phenotype. A growing appreciation for the existence of a variety of CD phenotypes has resulted in investigation to characterize potential risk factors for progression to medically complicated disease. Until a reliable method to achieve this goal is developed, clinicians will need to individualize treatment based on the extent of the disease at presentation and adjust their treatment approach according to response to such therapy and clinical disease progression.

Classically, conventional IBD therapy has used corticosteroids for the initial induction of remission in moderate-severe pediatric IBD. Salicylates have been used to maintain remission in UC and, despite the lack of convincing clinical trial data, in CD as well. The inability to achieve steroid-free remission for the majority of patients has led to the use of immunomodulators such as the thiopurines and methotrexate in more than 80% of pediatric CD patients within two years of diagnosis. Despite such treatment strategies, up to 30% of pediatric CD patients remain refractory or dependent on steroids one year after diagnosis. Most recently biologic therapies such as monoclonal antibodies against tumor necrosis factor alpha (TNFα) have emerged as important steroid-sparing agents that can both induce and maintain remission in moderate-severe childhood CD. The prototype of this class of therapeutic agents is infliximab.

This review is intended to provide clinicians with a general overview of the pharmacologic properties and function of infliximab. A clinically relevant discussion of infliximab’s use in pediatric CD including efficacy, various dosing regimens, patient selection and safety profile will also be included.

Pharmacokinetics
Infliximab is a chimeric, murine monoclonal IgG antibody against human TNFα. Infliximab binds to both the membrane bound and serum soluble forms of TNFα. The production of TNFα has been previously shown to be markedly increased within the mucosa of Crohn’s disease patients as well as there being increased levels in the serum of pediatric CD patients.

The therapeutic effect of infliximab has been attributed to multiple mechanisms of anti-inflammatory action via blockade of the TNFα cytokine pathway. Some of the important mechanisms previously demonstrated include: the effective down-regulation of pro-inflammatory cytokines, the reduction of activated leukocyte and lymphocyte migration, as well as inducing apoptosis of activated monocytes and T-lymphocytes. Standard infliximab infusion at a 5 mg/kg dose will often result in peak concentrations ranging from 100–190 µg/ml, while the maximum concentration (Cmax) remains dose dependent. After an infusion of 5 mg/kg of infliximab, levels become undetectable (<0.1 µg/ml) by week 12, with a reported serum half-life of 8–10 days. The serum clearance of infliximab does not appear to be reliant on any specific drug-metabolizing enzyme (i.e. cytochrome P450 enzyme super-families), but rather it is believed to be accomplished through degradation protease(s) that have yet to be identified. These combined pharmacokinetic properties have contributed to the now standard 8 week interval dosing of maintenance infliximab.

As a chimeric antibody, infliximab is immunogenic. The presence of antibodies to infliximab (ATI) has been shown to decrease the rates of clinical remission and to increase the occurrence of infusion reactions. A possible mechanism is that ATI have been shown to accelerate infliximab’s clearance and there is evidence that low infliximab trough levels are associated with decreased rates of clinical remission and mucosal healing in Crohn’s disease and Ulcerative Colitis. It has been shown that ATI formation may be significantly reduced by employing regularly scheduled infusions for maintenance therapy as opposed to episodic treatment. Similarly, the use
of concomitant immunomodulators is a recognized strategy to decrease ATI formation. Additionally the use of corticosteroids for prophylaxis has been demonstrated to reduce the rate and severity of infliximab infusion reactions and the median ATI serum concentration levels. Although it seems prudent to devise a strategy to maximize infliximab trough levels while minimizing ATI formation, the optimal serum trough level has not yet been defined and is likely to be patient dependent.

Efficacy in Pediatric Crohn’s Disease: The Evidence

One of the earliest reports of infliximab use in the pediatric population was published by Hyams et al. The authors conducted a retrospective evaluation of 19 patients with active intestinal Crohn’s disease who had received up to 3 doses (5 mg/kg) of infliximab over 12 weeks. The authors observed a rapid and sustained response to infliximab therapy through the 12 weeks. Corticosteroid use was also significantly decreased by week 12.

Kugathasan et al reported on 15 children enrolled in a prospective open-label trial of infliximab. The subjects were classified as having early or late Crohn’s disease. The study revealed that 14/15 children (94%) improved after infliximab infusion, with a significant decrease of the pediatric Crohn’s disease activity index (PCDAI) and daily steroid use by 4 weeks. The authors found a significant advantage to giving infliximab in the patients categorized as having early rather than late disease.

Baldassano et al conducted a randomized, open label, single-blinded trial of infliximab therapy in medically refractory moderate-severe pediatric CD. A total of 21 poorly controlled patients were randomized to receive infliximab at 1 mg/kg, 5 mg/kg, and 10 mg/kg doses. The highest response rates were seen with the 5 mg/kg and 10 mg/kg dose and at 12 weeks, 48% of the patients achieved clinical remission. The authors concluded that infliximab is a safe and effective short-term therapy for medically refractory moderate-severe pediatric CD patients.

The steroid sparing effects of infliximab in pediatric CD were demonstrated in several recent reports. Markowitz et al presented data from a retrospective review of 109 children with luminal CD. In this cohort, 30 were observed to be corticosteroid resistant or dependent and started on infliximab. After one year of follow up, 16/24 (67%) of these patients had discontinued all corticosteroid use, irrespective of the duration of prior steroid exposure. Similarly, a prospective multicenter cohort from France reported on 21 patients who received infliximab for the treatment of pediatric CD. The authors observed marked improvement in clinical outcomes, with 14/21 (67%) of the patients discontinuing corticosteroids at 3 months, and all 12 patients with perianal fistulas exhibiting complete healing. Notably, without ongoing infliximab use, the authors found that 90% of the patients relapsed at by one year of follow up again supporting the use of ongoing, scheduled infusions of infliximab.

The randomized, multicenter, open-label study to evaluate the safety and efficacy of infliximab in pediatric subjects with moderate-to-severe Crohn’s disease (REACH) study was the prospective clinical trial that led to official licensure of the agent in pediatric CD. The trial was designed to evaluate the efficacy of a 3 dose induction regimen of infliximab 5 mg/kg at 0, 2, and 6 weeks, as well as to assess the efficacy of maintaining clinical remission at week 54 using two different maintenance arms of every eight week versus every 12 week dosing. The study included 112 patients with moderate-severe CD, all of whom were concomitantly on immunomodulator or steroid therapy. At week 10 it was observed that 99 (88.4%) of the patients had a clinical response to the induction regimen, as defined by a decrease in the PCDAI score ≥15 points. The responders were then randomized to receive infliximab at 8 or 12 week intervals. At the week 54 assessment 33/52 (63.5%) of the 8 week interval group vs. 17/51 (33.3%) of the 12 week interval group continued to exhibit clinical response (p = 0.002). Similarly after 54 weeks of therapy 29/52 (55.8%) of the 8 week interval group vs. 12/51 (23.5%) of the 12 week interval group were in clinical remission, as defined by a PCDAI score ≤10 (p < 0.001). Among the patients who were using corticosteroids at baseline, 45.8% of those in the 8 week interval group and 16.7% of those in the 12 week interval group had discontinued their use at week 30 and remained in clinical remission at the 54 week evaluation. The authors concluded that pediatric patients with moderate-severe CD who responded to
infliximab induction were more likely to continue to experience clinical response and remission at week 54 when given infliximab at 8 week interval as compared to 12 week intervals.

A recent post-hoc analysis of the REACH trial by Crandall et al looked at 22 patients with peri-anal disease at baseline. At 54 weeks 72.7% (16/22) of the patients had significant improvement in the signs and symptoms of perianal disease (1 with partial and 15 with complete healing). The authors also note that although infliximab therapy did not prevent the development of perianal disease, after 54 weeks of treatment 77.7% (7/9) patients attained a complete response.

Recently Hyams et al provided long-term data on the use of infliximab to treat pediatric CD. This was a multi-center cohort study of 128 pediatric patients with CD who received infliximab maintenance therapy for a median of 3.5 years. Over the course of study, the rates of sustained clinical response and remission in pediatric patients with luminal CD who were treated with infliximab were significantly superior to those receiving corticosteroids or immunomodulators alone (65% versus 28% at one year; 73% versus 45% at two years, and 83% versus 30% after 3 years respectively). Sustained clinical response was defined as a physician global assessment (PGA) of mild or inactive disease at every assessment point during follow-up while receiving infliximab without concomitant corticosteroid use or surgery. Sustained clinical remission was defined as a PGA of inactive disease at every assessment point during the period of follow-up while receiving infliximab without concomitant corticosteroid use or surgery. Similarly after 1, 2, or 3 years of therapy less than 10% of the patients required corticosteroid therapy as compared to over 50% prior to starting infliximab. To achieve this long-term successful treatment with infliximab, dose adjustments were required in 63/128 (49%) of the study patients with 32% requiring an increase in dose concentration and 17% necessitating decreased intervals between infusions.

In the spring of 2006 the US FDA approved infliximab for the induction and maintenance of remission for moderate-severe pediatric CD in patients who are unresponsive to conventional therapy. The optimal dosing strategy and patient selection for this therapy still need further investigation in order to properly balance the risk of adverse events versus the drug’s efficacy. Some of the issues of proper dosing and patient selection will follow.

**Monotherapy Versus Combination Immunomodulators**

A hotly debated topic is whether to use infliximab in combination with an immunomodulator or as monotherapy. Currently infliximab is approved for use in a select pediatric CD population who has failed the so-called conventional therapy. Therefore, by necessity, infliximab has been used as a later-line therapy, usually after immunomodulators have been used. Early common practice was to continue immunomodulator therapy with the infliximab.

A potential benefit of combination therapy would be to minimize infliximab’s immunogenicity and thereby increase infliximab trough levels and the drug’s efficacy. Despite the data suggesting a correlation between infliximab trough levels and clinical outcomes, the matter remains controversial. Furthermore, a rare but incurable form of non-Hodgkin’s lymphoma (hepatosplenic T-cell lymphoma or HSTCL) has been reported in the pediatric population receiving combination thiopurines and infliximab therapy. The potential for such a significant adverse outcome has raised questions about the risk: benefit ratio of combination immunosuppressive therapy.

A recent trial published in abstract form suggests that combination therapy may be advantageous in treatment-naíve patients with early disease. The authors blindly randomized 508 patients into a three arm study consisting of treatment with azathioprine plus placebo, infliximab plus placebo, or infliximab plus azathioprine. After 52 weeks of follow up, there was a 46% steroid free remission rate with infliximab plus azathioprine versus 35% with infliximab alone (p = 0.035). Similarly the proportion of patients with mucosal healing at week 26 was 44% with infliximab plus azathioprine versus 30% with infliximab (p = 0.055). The authors conclude that treatment “naíve” patients with moderate-severe Crohn’s disease may have greater benefit with early combined biologic and immunomodulator therapy.

The question as to how long concomitant immunomodulator therapy needs to be continued was
addressed by Van Asshe et al who reported on a prospective trial of 80 adult patients. In this trial, after 6 months of combination infliximab and other immunomodulator therapy, participants were randomized to either continue combination therapy or infliximab alone. After two years of follow up, the authors found that there were no significant differences in clinical outcomes including mucosal healing rates between the combination and monotherapy groups. The authors concluded that continuation of immunosuppressive combination therapy beyond 6 months offers no clear benefit over scheduled infliximab monotherapy. Similarly a prospective randomized trial comparing infliximab monotherapy vs. combination methotrexate and infliximab in adult patients who have undergone therapeutic induction with corticosteroids demonstrated equal efficacy in both groups. In the (COMMIT) trial, Feagan et al reported that after one year of follow up, remission rates in patients who initially required corticosteroids for induction therapy were not statistically different between combination infliximab and methotrexate versus infliximab alone. It is important to point out that SONIC, and the Van Asshe and COMMIT trials involve adult patients and that and trials larger long-term pediatric trials will be necessary before any clear conclusive evidence may be demonstrated.

Although monotherapy with infliximab alone appears to be an attractive and efficacious treatment regimen for Crohn’s disease, as of yet consensus on concomitant therapy with immunomodulators and biologics does not exist. A recent abstract presented by Melmed et al describes their application of the validated RAND/UCLA appropriateness method toward determining the appropriateness of simultaneous immunomodulator and anti-TNF-α therapies. After a comprehensive review of the literature the authors describe reaching an expert panel consensus on the “appropriateness” of combination therapy in 63 scenarios including, extensive disease, perianal involvement, history of prior surgery, short duration of disease, and age >26. Concomitant therapy was agreed upon being “inappropriate” particularly in young males, and some scenarios of uncomplicated disease. While the literature continues to evolve regarding Various clinical benefits of combination therapy versus monotherapy, the use of an anti-TNF-α alone is confounded by the fact that most patients are started on biologies only after having “failed” conventional therapies including immunomodulators. Perhaps an even more clinically relevant question would be the timing of biologic therapy: should we use such agents as a first step in the treatment of moderate-severe Crohn’s disease?

Is it too soon or not soon Enough? Patient Selection

Currently the use of anti-TNF therapy is reserved for patients with moderate-severe CD who are deemed “unresponsive” to conventional therapies. The definition of “unresponsive” primarily relies on clinical judgment rather than the fulfillment of strict criteria. Consequently, physicians are left with the task of deciding which patients should be started on such therapy. Traditional medications such as steroids and immunomodulators are often seen as the “safer” class of medications and by convention tend to be the first line of treatment, while patients whose symptoms continue to worsen or fail to attain remission may be moved up to biologic therapy. This approach is often referred to as the “step up” method.

The uniqueness of the pediatric patient is the need to develop treatment protocols that balance the risk to benefit ratio of CD therapy while considering the effect on height velocity as well as overall growth and development. Additionally, as is the case for any chronic condition, treatment for Crohn’s disease is designed to achieve a rapid remission of acute symptoms while, hopefully, positively affecting the natural history of the disease. A particularly revealing review was reported by Cosnes et al on 25 years of experience with 565 patients who, despite receiving immunomodulators with increasing frequency, exhibited unchanged rates of developing stricturing or penetrating intestinal complications requiring resection. Additionally, population based studies have shown that conventional therapy achieves clinical remission in only 42% of Crohn’s disease patients at two years and 12% at ten years after diagnosis. The need for therapies that yield higher rates of durable remission is one that is quite clear to anyone involved in the care of patients with IBD.
The “step-down” approach is a term used for the early intervention with anti-TNF therapies and other emerging agents. There is evidence demonstrating potential clinical advantage to starting patients early on biologic therapy. The previously discussed SONIC trial showed greater efficacy in patients who were started early on combination immunomodulator and biologic therapy. Similarly, the above mentioned COMMIT trial showed positive outcomes in patients who where maintained on infliximab for a year after steroid induction. D’Haens et al reported an open label, prospective randomized clinical trial conducted across 18 medical centers. The authors randomized 133 patients to receive either infliximab and azathioprine for induction followed by azathioprine maintenance therapy alone (“step-down”) versus induction with corticosteroids followed successively by azathioprine maintenance and episodic infliximab as needed (“step up”). After 52 weeks of follow up 61.5% of the “step-down” group where in remission versus 42.2% of the “step-up” group (absolute difference 19.3%, 95% CI 2.4–36.3, p = 0.0278). After two years of follow up the “step-down” group also demonstrated significantly higher rates of mucosal healing (73.1% vs. 30.4% p = 0.0028).36

There is also preliminary evidence that the early use of anti-TNF therapy may have greater clinical efficacy in pediatric CD patients. A similar study reported in abstract form37 randomly assigned 32 pediatric patients with ileocecal disease to receive infliximab followed by thiopurines or methotrexate for induction versus nutritional therapy or corticosteroids for induction followed by the same maintenance regimen. At the 12 month follow up, patients who received infliximab therapy for induction had significantly higher remission rates and mucosal healing.

Anti-TNF therapy may have the greatest impact on important pediatric end-points including quality of life and growth. In the previously described REACH trial24 the authors’ secondary endpoints included the assessment of quality of life, as measured by the IMPACT III questionnaire (a validated 35-item self administered questionnaire). It was found that at both 10 and 54 weeks, patients who received infliximab therapy had a significant increase in quality of life score (p = 0.001). Furthermore, significant growth improvement was seen with infliximab therapy, increasing the Z-score by a mean of 0.5 from baseline (95% CI 0.3 to 0.7) during the 54 weeks of follow up.

It appears that early use of biologic agents may confer better clinical outcomes in pediatric patients with Crohn’s disease. Clearly, more long-term prospective follow-up is necessary to clarify which patients will enjoy better remission and luminal healing rates, improved height velocity and overall quality of life with an acceptable rate of side effects.

Safety of Infliximab Treatment

As a chimeric murine antibody, some of the commonly encountered side effects of infliximab can be attributed to its immunogenic potential. Patients may experience both acute and delayed infusion reactions. Acute reactions may include symptoms such as headache, nausea, chest pain, dizziness, urticaria, shortness of breath, and rarely anaphylactic shock and laryngeal edema.38 Delayed reactions normally occur several days to weeks after an infusion, and may be seen after a single dose or after more prolonged treatment. A delayed reaction may include symptoms of arthralgias, peripheral edema, dysphagia, headache, and pruritis. As discussed earlier there is ample evidence that infusion reactions are related to ATI formation and may be reduced with regularly scheduled maintenance therapy as well as concomitant immunomodulator therapy. The reported incidence of these reactions has ranged from 3%-4% of infliximab treatments.39

The utility of pre-medication, defined as antipyretics, antihistamines, and corticosteroids, in preventing infusion reactions was investigated in a cohort of 243 pediatric patients with IBD and reported by Jacobstein et al. The authors observed that the administration of any of the above mentioned medications did not prevent the first occurrence of infusion reactions; however their use did significantly reduce the recurrence of infusion reactions during subsequent treatments.40

As an immunosuppressive therapy, infectious complications remain a concern. The REACH trial reported an infection rate of 56% among its 112 pediatric participants. The majority (35%) of these infections were mild upper respiratory infections. More serious infections included herpes zoster in 2%, pneumonia in 3%, and abscess in 5% of the patient population.44 Another significant infection, not uncommonly reported with infliximab therapy, is the reactivation of latent tuberculosis. Therefore intradermal purified protein (PPD) testing is required in all patients prior to initiation of therapy.
to starting infliximab therapy. The high incidence of patients exhibiting anergy to PPD testing also requires physicians to stringently assess TB exposure risks factors and consider obtaining a chest x-ray in appropriate cases.41

The incidence of lymphoma in patients with known IBD has been extensively investigated and it has remained controversial whether IBD itself increases this risk. A recent population based, prospective study in Sweden was designed to look at this issue. The investigators evaluated 47,000 patients with IBD for the incidence of hematopoietic cancer. The risk of disease related lymphoma seemed highest in the relatively young population soon after diagnosis. As the cohort aged, the risk became similar to that of the general population.42 In addition to the question as to whether the disease itself increases lymphoma risk, it has been observed that there are excess lymphomas in IBD patients who have received immunomodulator as well as biologic therapies. A critical study that established the risk of lymphoma in adult IBD patients receiving immunomodulators was reported by Kandel et al. The authors demonstrated approximately a fourfold increased risk of lymphoma in IBD patients treated with thiopurines.43 A similar finding reported by the CESAME study group evaluated 20,000 adult patients with IBD; the authors concluded that the hazard ratio of developing a lymphoproliferative in patients receiving thiopurines 5.28 (95% CI 2.01–13.9, p = 0.0007).44 Although similar data has not yet been generated in the pediatric population, physicians may evoke the above mentioned information when counseling CD patients receiving immunomodulator therapies.

Regarding potential malignancy risk and infliximab therapy, there is a recently published meta-analysis that evaluated 8905 patients equaling 21,178 patient years of follow-up. When compared with the expected rate of non-Hodgkin’s lymphoma in the surveillance epidemiology and end results (SEER) database (1.9 per 10,000 patient-years), anti-TNF treated subjects had a significantly elevated risk (SIR, 3.23; 95% CI, 1.5–6.9). When compared with the NHL rate in patients treated with immunomodulators alone versus biologics alone the SIR was only slightly greater at 1.7 (95% confidence interval, 0.5–7.1). It is important to note that of the 13 anti-TNF treated patients who were reported to develop NHL, 10 had also received immunomodulator therapy, with the effect of this combination therapy likely contributing to the increased risk of malignancy.45

Similar long-term follow up in a large pediatric CD cohort is still needed before the possible malignancy risk can be more accurately established. While the medical community is awaiting a definitive link between biologic therapy and increased risk of malignancy, a rare form of non-Hodgkin’s lymphoma has been reported in 18 pediatric patients who have received concomitant infliximab and immunomodulator therapy.30 It is important to point out that a similar number of cases of HSTCL have been reported with thiopurine monotherapy9 raising the question as to which is truly the safer therapy. Nonetheless, even though the risk of developing hepatosplenic T cell lymphoma (HSTCL) has been reported to be exceedingly low, this malignancy remains uniformly fatal and has led to a black box warning regarding malignancies and the use of infliximab in pediatric patients. It is at least in part for this reason that the makers of infliximab have established a registry to collect prospective data concerning infliximab administration in pediatric Crohn’s disease.

**Conclusion**

As the first anti-TNF alpha therapy approved for the treatment of pediatric Crohn’s disease, infliximab has ushered in a new line of therapeutic options. Through continued clinical investigation this therapeutic class has already established itself as highly efficacious in achieving and maintaining clinical remission, mucosal healing, improved growth velocity and improved quality of life in pediatric Crohn’s disease patients. Although the role of biologics as first line therapy in moderate-severe pediatric CD is starting to be discussed, conventional therapies remain the first line choice for most clinicians. Currently the decision of which patients would most benefit from starting infliximab therapy, whether it is best used alone or in combination, and whether to start treatment early or late in the disease progression remains in the realm of clinical judgment more than evidence-based approach. Furthermore, the use of biologic therapy remains constrained by its potential risk of immunogenic, infectious and rarely, malignant complications.

As ongoing studies continue to expand our understanding of the natural history of pediatric Crohn’s
disease, we are likely to achieve better characterization of the genotypic and/or phenotypic influences on therapeutic response rates. This better understanding will allow for more personalized treatment based on an individual’s unique form of Crohn’s disease.

Disclosures
This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. Joel Rosh has the following disclosures: Research Grant Support: Abbott, Centocor, UCB. Consultant/Advisory Board: Abbott, Centocor, UCB. Speakers’ Bureau/Honorarium: Abbott Nutrition.

References
Infliximab in pediatric Crohn’s disease


---

**Publish with Libertas Academica and every scientist working in your field can read your article**

“I would like to say that this is the most author-friendly editing process I have experienced in over 150 publications. Thank you most sincerely.”

“The communication between your staff and me has been terrific. Whenever progress is made with the manuscript, I receive notice. Quite honestly, I’ve never had such complete communication with a journal.”

“LA is different, and hopefully represents a kind of scientific publication machinery that removes the hurdles from free flow of scientific thought.”

Your paper will be:

- Available to your entire community free of charge
- Fairly and quickly peer reviewed
- Yours! You retain copyright

http://www.la-press.com