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Refractory autoimmune disease: an overview of when first-line therapy is not enough

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ABSTRACT

A recent Intercontinental Cooperative ITP Study Group (ICIS) meeting in September 2015 focused on immunomodulation across the spectrum of autoimmune conditions. It became clear to the attendees that in this wide range of conditions, there is a subset of patients that remain highly refractory to first line therapy. Therapeutic approaches to these patients vary greatly and while many different immunomodulatory agents have been investigated, few have seen universal success. We outline here the landscape of immunomodulation therapy for refractory patients across a variety of autoimmune conditions in order to highlight the variety of agents that have been studied, the lack of overall consensus about management, and the need for ongoing research in this area.

Many autoimmune conditions are treated with a backbone of immunomodulatory and immunosuppressive therapy. These include but are not limited to rheumatologic conditions such as juvenile idiopathic arthritis (JIA), gastroenterologic conditions such as inflammatory bowel disease (IBD), neurologic conditions like multiple sclerosis (MS), dermatologic conditions such as psoriasis, and hematologic conditions such as immune thrombocytopenia (ITP) and autoimmune hemolytic anemia, to name a few.

A recent Intercontinental Cooperative ITP Study Group (ICIS) meeting in September 2015 focused on immunomodulation across the spectrum of autoimmune conditions. It became clear to the attendees that in this wide range of conditions, there are commonalities in patient groups by response to treatment; with a subset of patients being refractory to first-line therapy regardless of the disease in question. For these patients many new therapeutic options are becoming available without substantial evidence based data about immediate and long-term outcomes. This has lead to increased difficulty identifying the ideal agent for individual patients and an absence of overall consensus [1-4]. Much of this difficulty stems from a lack of understanding of the multi-factorial and complicated pathogenesis of autoimmunity, and how this relates to the clinical heterogeneity of the disease, making targeted drug therapy challenging. We provide here an overview of the challenges facing refractory patients using ITP, MS, IBD, and JIA as examples.

1. Immune thrombocytopenia

In the majority of patients with ITP first-line agents, including corticosteroids, anti-D immunoglobulin, and intravenous immunoglobulin [1], are effective at increasing the platelet count and reducing bleeding symptoms. There remains however a handful of patients who either fail first-line therapy or have persistent or chronic disease requiring second-line therapy despite an initial transient response. Management of these patients can prove highly challenging and while many immunomodulatory options exist very few have resulted in substantial cure rates. Furthermore, most of the evidence for these agents is derived from small observational studies.

Response rates to second-line immunomodulatory therapy in ITP are shown in Table 1. Approximately half of patients treated with a second-line drug therapy will have a complete response. Unfortunately, there are no identifiable biological or clinical predictors of response to help guide clinicians with selecting an agent. Also little is known about the durability of response given the short and variable follow-up of clinical investigations. For many second-line ITP agents even if the initial response rate looks promising a majority of patients relapse shortly after receiving

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Table 1
Second-line immunomodulatory therapies for ITP.

Agent	No.	Response rate
Azathioprine [38]	53	51%
Cyclosporine [39]	14	50%
Cyclophosphamide [40]	20	85%
Danazol [41]	57	67%
Dapsone [42]	66	50%
Mycophenolate mofetil [43]	21	63%
Rituximab [7]	376	57%
Vinca alkaloids [44]	43	47%

therapy [2]. In addition, some agents require ongoing long-term therapy in order to maintain a response making them less desirable over time. One of the most well studied second-line agents in ITP is rituximab. While, at first a promising agent, with initial induction rates of 60%, more recent data suggest that only 26% of treated patients remain in remission 5 years following treatment, highlighting the difficulty in achieving long-term success with second-line agents [5–7]. Also this stresses the importance of long-term follow-up data in clinical trials to examine the real therapeutic contribution of these agents.

Additional non-immunosuppressive approaches for treating refractory patients with ITP have been developed. Thrombopoietin- receptor agonists (TPO-RAs) are a class of medications that induce platelet production to overcome the peripheral antibody destruction. Two agents, romiplostim and eltrombopag, are approved by the US Food and Drug Administration (FDA) for adults with chronic ITP and eltrombopag is also approved for children ≥ 1 year of age with chronic ITP. Both of these agents have been shown to be effective in clinical trials; however, because they do not directly address the underlying immune dysfunction in most patients, the effect is lost once the agent is discontinued [8–18].

2. Multiple sclerosis

The same general picture appears to be true based on data in MS. Much like ITP, a subset of patients fail first-line therapies, continue to relapse, or undergo transformation to progressive disease (approximately 50%–80% within 20–25 years from diagnosis) [19,20]. An additional 10%–18% of patients have a diagnosis of progressive disease from the onset [20,21]. Due to failure of existing therapies at addressing patients with progressive disease an International Progressive MS Alliance has been form to accelerate novel drug therapy development for this indication [22]. Current options for second-line therapies addressed in a recent Cochrane review include natalizumab, mitoxantrone, fingolimod, teriflunomide, alemutuzumab, daclizumab, and ocrelizumab, azathioprine, and intravenous immunoglobulin. The Cochrane review investigated the relative effect of these agents compared to placebo in patients with relapsing remitting MS. Based on the chance of experiencing one or more relapses over 12 months these agents showed a relative effect that ranged from 0.40 to as high as 0.87 [19]. However, it is important to note that the confidence in the evidence was consistently low, follow-up was brief and primary outcomes were variable. Furthermore, these agents have not shown efficacy in preventing the formation of progressive disease or halting it once it has begun [20].

3. Inflammatory bowel disease

The therapeutic landscape is similar in patients with IBD where medical therapy is becoming more complex. First-line treatments in Crohn's disease (CD) include systemic corticosteroids such as methylprednisolone and topical corticosteroids such as budesonide, which can reduce the intestinal inflammation [23]. Aminosalicylates such as mesalazine or sulfasalazine are used as first-line treatment in ulcerative colitis (UC). Immunomodulators, such as azathioprine, 6-mercaptopurine and methotrexate can provide control of the immune response in patients not sufficiently responding to first-line treatments [23]. Up to 40% of patients with CD may require biologics; however, only 30%–50% achieve complete remission after 6 months and 30% are able to maintain the response for 12 months [4]. Current strategies to overcome loss of response include development of novel therapeutics including anti-tumor necrosis factor (TNF) therapies, anti–interleukin-6 (IL-6), anti-integrins, anti-chemokine, and IL-10 agents [24]. Infliximab, adalimumab, and certolizumab pegol are anti-TNF agents that are licensed for patients with CD who are intolerant of or have failed conventional therapy, with remission rates of approximately 30%–50% [24]. Even lower response rates, 20% at 1 year following infliximab, adalimumab, or golimumab treatment, have been seen in patients with UC [24]. Anti–IL-6 therapies, while showing early remission rates as high as 80%, have been associated with fatalities due to suppression of C-reactive protein levels leading to missed infectious complications [24]. Vedolizumab is the first anti-integrin antibody to be approved for the therapy of CD and UC, with response rates of 47% in UC but only 14% in patients with CD after 6 weeks [24]. Remission rates increase further after 8 and 10 weeks indicating that anti-integrins need a long time to achieve therapeutic effect. Both anti-chemokine and IL-10 strategies have not shown significant effects in patients with IBD. The preliminary data for mongersen, a Smad7 antisense oligonucleotide, are promising with response rates of $>50\%$; however, some concerns exist over the long-term effect of transforming growth factor (TGF)-β induction on fibrosis formation [24]. Lastly, tofacitinib, a small molecule JAK inhibitor, has demonstrated early remission rates of 61%–78%; however, by 8 weeks the response rate had declined to 41% [24]. Based on these new developments treatment algorithms need to be updated and therapy benefit will need to be closely weighed against risks.

4. Juvenile idiopathic arthritis

Rheumatic diseases in children represent another category of pathologies in which immunomodulation is a predominant aspect of treatment and refractory patients posed a challenge. Data suggest that at 10 years only 33% of patients are without disease activity in the absence of antirheumatic therapy for at least 6 months; this number is even lower (24%) in patients with polyarticular disease. The classic therapies include nonsteroidal anti-inflammatories, corticosteroids, and nonbiologic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX), leflunomide, and sulfasalazine. Despite first-line therapy up to 30% of patients with polyarticular JIA will continue to have active disease. The revolutionary introduction of biological therapies in 1999 led to dramatic improvements in the prognosis for these pediatric patients and the goal shifted from simple analgesia to disease inactivity and prevention of disability [25].

Biological therapies target pro-inflammatory cytokines or cell surface antigens and include monoclonal antibodies (mAb) and soluble receptors. The earliest pathogenic biologic target defined in JIA is TNF-α. This proinflammatory cytokine was found in increased levels in the serum and synovial fluid of children with JIA [26]. Etanercept, a fusion protein that binds circulating TNF, was the first US FDA approved biologic for the treatment of DMARD resistant polyarticular JIA. Its efficacy was proven in a multicenter, randomized, placebo-controlled trial with 28% versus 74% flares in treatment and placebo arms, respectively [27].