

## Immune-Mediated Inflammatory Disorders (I.M.I.D.s): The Economic and Clinical Costs

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### Abstract

Immune-mediated inflammatory disorders (I.M.I.D.s) are a group of diseases that involve an immune response that is inappropriate or excessive, and is caused, signified, or accompanied by dysregulation of the body's normal cytokine milieu. I.M.I.D.s cause acute or chronic inflammatory injury, sometimes severe, in any organ system. Despite strong evidence linking the pathophysiologies and treatments of the diseases that constitute the I.M.I.D. group, providers, payers, employers, and benefits consultants have been slow to adopt the I.M.I.D. concept. As a result, these stakeholders risk underestimating the significant clinical and economic burdens of the I.M.I.D. class. In this review we examine those burdens, specifically analyzing I.M.I.D. prevalence and cost data for a group of large employers. We also describe the scientific rationale for the I.M.I.D. paradigm, examine the cytokine dysregulation that many I.M.I.D.s share, and focus in detail on the pathophysiology of 3 I.M.I.D.s with high morbidity: rheumatoid arthritis, Crohn's disease, and type 1 diabetes mellitus. The review concludes with an evaluation of approved anticytokine I.M.I.D. therapies and those in development.

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The concept of autoimmune disease has existed for at least 100 years, and there has been biochemical evidence of these conditions' shared mechanisms for at least 15 years.<sup>1,2</sup> Dysregulation of cytokines, a group of small proteins produced ubiquitously in the body, has proven to be a key element

in these shared mechanisms. In the last 5 years, anticytokine therapies have produced therapeutic breakthroughs in conditions ranging from rheumatoid arthritis (RA) to Crohn's disease (CD). Nevertheless, despite shared pathophysiology and therapy, autoimmune conditions are not typically seen as interrelated by payers, providers, employers, and benefits consultants (personal communication, P. Lopatka, July 2002). For example, RA is usually considered a rheumatological disorder and CD a gastrointestinal condition, even though the cytokine dysregulation and treatment of each illness may be similar.<sup>3</sup>

This review describes a new medical paradigm—the immune-mediated inflammatory disorders (I.M.I.D.s)—that will help healthcare stakeholders understand the economic and clinical burden of a group of diseases that together may affect as much as 5%-7% of the American population.<sup>1,4</sup> I.M.I.D.s involve an immune response that is inappropriate or excessive and is caused, signified, or accompanied by a dysregulation of the normal cytokine milieu. They also cause acute or chronic inflammatory injury, sometimes severe, in any organ system.

Many illnesses fulfill these criteria, from the relatively obscure, such as giant cell arteritis, to public health crises, such as type 1 diabetes mellitus (T1DM). For payers, it is helpful to focus on the conditions that have the highest per-member-

per-year (PMPY) cost, which takes into account prevalence of the disease and claims per patient. Before discussing I.M.I.D.s, however, it makes sense to briefly consider what exactly cytokines are and how their dysregulation can lead to pathophysiology.

### **What Are Cytokines and Why Do They Matter?**

Cytokines are a family of proteins and polypeptides that are secreted by many different cell types and that are required for physiological immune function, inflammation, cell growth, and tissue repair.<sup>3</sup> Cytokine dysregulation, however, can lead to I.M.I.D.s.<sup>5</sup> In some cases cytokine overproduction may be associated with I.M.I.D. pathophysiology, as in rheumatoid arthritis and Crohn's disease.<sup>4,5</sup> Underproduction of cytokines may also be seen in certain I.M.I.D.s, as in systemic lupus erythematosus.<sup>4</sup> To make matters even more complicated, over- or underproduction of certain cytokines may have different effects, depending on where, when, and in what tissue microenvironments the dysregulation occurs.<sup>5</sup> Additionally, blocking or augmenting cytokine action through pharmacotherapy may reduce inflammation—or may have an unintended proinflammatory effect.<sup>6</sup>

As a general rule, it is helpful to think of cytokines as having proinflammatory or anti-inflammatory characteristics. The cytokines interleukin 1 (IL-1), interleukin 2 (IL-2), interleukin 12 (IL-12), interferon  $\gamma$  (IFN- $\gamma$ ), and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) are typically proinflammatory, whereas the cytokines interleukin 4 (IL-4), interleukin 10 (IL-10), and transforming growth factor  $\beta$  (TGF- $\beta$ ) are often anti-inflammatory.<sup>3,5,7-14</sup> These cytokines generate many of their pro- and anti-inflammatory effects through their actions on a group of immune cells known as helper or CD4+ T lymphocytes.

These helper T cells comprise 2 subsets: Th1 and Th2.<sup>15</sup> The Th1 cells have been associated with the development of I.M.I.D.s, and the Th2 cells may suppress their development. Cytokines steer devel-

oping helper T cells down the Th1 or Th2 paths, and cytokines produced by the Th1 subset tend to be proinflammatory, with Th2 cytokines typically being anti-inflammatory.<sup>16</sup> It should be noted, however, that recent investigations have shown that the Th1/Th2 paradigm may be incomplete. First, just as typically proinflammatory cytokines may sometimes be anti-inflammatory and anti-inflammatory cytokines may be proinflammatory, Th1 cells may sometimes have an anti-inflammatory effect, and Th2 cells a proinflammatory effect.<sup>5</sup> Second, a new class of helper T cells known as Th3 has recently been identified, and there may be other undescribed classes.<sup>17</sup>

Although the molecular biology of T cell differentiation is complex, it is worth examining, as many of the involved cytokines have offered and will offer important therapeutic targets. Simplified, the process works as follows: IL-12 causes differentiation of helper T cells into the Th1 proinflammatory subtype.<sup>18</sup> The Th1 cells then produce IL-2, which activates other T cells, and IFN- $\gamma$ , which causes additional IL-12 production, which in turn leads to more Th1 differentiation.<sup>14</sup> Although not produced by T cells, IL-1 causes the production of IL-2 by T cells and the synthesis of TNF- $\alpha$  by many different cell types.<sup>19,20</sup> TNF- $\alpha$  causes the production of more IL-1 and the activation of more T cells, creating an inflammatory feedback loop.<sup>20</sup> As will be shown shortly, overproduction of these cytokines has been associated with a number of I.M.I.D.s.<sup>4</sup> In contrast, IL-4 and IL-10 lead to the differentiation of helper T cells into the Th2 anti-inflammatory subtype and to the suppression of Th1 proinflammatory development.<sup>21</sup> TGF- $\beta$ , produced by a variety of cells, causes the production of IL-10, which further steers T cells into Th2 differentiation.<sup>21</sup>

### **Cytokines and I.M.I.D.s: What's the Connection?**

As stated above, dysregulation of cytokines can lead to the tissue damage associated with I.M.I.D.s. But how exactly does it happen? This review will examine

the process in 3 I.M.I.D.s with significant clinical and economic burdens: rheumatoid arthritis, Crohn's disease, and type 1 diabetes mellitus.

**RA: The Arche-typal I.M.I.D.** RA is a chronic, destructive arthropathy that disables as many as 80% of its sufferers.<sup>22</sup> Small joint destruction proceeds at 2%-3% per year, and after 20 years of disease, 23% of patients have near-total joint destruction in their hands and feet.<sup>23</sup> The degenerative process, however, extends beyond the small joints, and RA may involve the cervical spine in approximately half of patients.<sup>24</sup>

Most important, RA is a systemic disease that causes substantially increased mortality, especially due to cardiac disease.<sup>25,26</sup> Specifically, it has been postulated that the inflammatory milieu of RA leads to increased atherosclerosis.<sup>27</sup>

RA's social costs are dramatic. As many as 10% of patients quit their jobs within 3 years of disease onset, and those patients with the most severe disease can expect a 60% decline in earnings during the first 6 years of illness.<sup>28,29</sup> In addition, the divorce rate of those with RA is said to be 70% higher than that of the general population.<sup>29</sup>

The pathogenesis of RA is not completely understood. For example, it is likely that RA's inflammatory process is initiated by an arthritogenic antigen, possibly of bacterial origin, but the antigen's identity is currently unknown.<sup>30,31</sup> That antigen activates helper T cells of the Th1 subtype, which subsequently secrete or cause to be secreted an array of cytokines that indirectly leads to joint inflammation and destruction.<sup>22,32</sup>

It was observed more than a decade ago that significant amounts of IL-1 and TNF- $\alpha$  are found in the joint spaces of RA patients, but not in those of normal controls.<sup>33,34</sup> In addition, an early transgenic mouse study showed that mice constitutively expressing TNF- $\alpha$  developed a chronic arthritis and that this arthritis could be stopped by treatment with antibodies against TNF- $\alpha$ .<sup>35</sup> It is now thought that T cells, once activated in RA,

induce other cells to produce IL-1 and TNF- $\alpha$ , as well as an additional proinflammatory cytokine, interleukin-6 (IL-6).<sup>36,37</sup> Further, IL-1 and TNF- $\alpha$  further activate the T cell response, as well as lead to the secretion of destructive enzymes that erode the joint space.<sup>22,38</sup>

A number of cytokines, such as IL-4, IL-10, and TGF- $\beta$ , may play an anti-inflammatory role in RA.<sup>21</sup> IL-10, for example, is one of the key cytokines that steers T cells toward the anti-inflammatory Th2 pathway, and it can be detected in the joint fluid of RA patients.<sup>39</sup> IL-4 and IL-10 lead to the formation of a naturally occurring IL-1 receptor antagonist that acts as a kind of molecular sponge for IL-1.<sup>40</sup> In addition, when IL-10 activity is blocked in patients with RA, secretion of proinflammatory cytokines TNF- $\alpha$  and IL-1 increases.<sup>41</sup>

These findings demonstrate that RA fits the I.M.I.D. paradigm. As defined in the beginning of the review, an I.M.I.D. involves an immune response that is inappropriate or excessive. Although the trigger for this immune response remains unknown, there can be no doubt that severe autoimmunity does occur in RA and involves the widespread activation of immune cells. In addition, with RA there are significant alterations in the physiological cytokine profile of the joint space that correlate with and may sometimes cause the immune response. Most importantly, this cytokine-driven immune response causes devastating injury to the host.

**CD: Is It RA of the Gut?** Crohn's disease (CD) is a chronic condition that involves severe, asymmetric inflammation throughout the gastrointestinal tract, as well as extragastrointestinal manifestations in the skin, eyes, and joints.<sup>42</sup> Like RA, CD is a systemic disease. One epidemiological study showed that after 20 years of disease, 26% of CD patients developed perianal fistulae, and 23% of those fistulae required bowel resection.<sup>43</sup> The incidence rates of liver/biliary tract and small bowel carcinoma in CD patients are, respectively, 5.2 and 17.4

times greater than the incidence rates of those cancers in the general population.<sup>44</sup> Not surprisingly, depression and anxiety are significantly more common in CD patients after diagnosis than before.<sup>45</sup>

Neither the cause nor the complete pathogenesis of CD is known, although a gene mutation on chromosome 16 is more than twice as likely to occur in CD patients as in controls.<sup>46</sup> Like RA, CD appears to be set in motion by an inappropriate or excessive immune response, potentially to intestinal bacteria. For example, mice deficient in the anti-inflammatory cytokine IL-10 develop a CD-like condition—unless they are maintained in a germ-free environment.<sup>47</sup>

In normal individuals, subpopulations of T cells, supported by IL-10, prevent an immune response against gut bacteria, but this regulation appears to be disrupted in CD.<sup>48</sup> In addition, the balance of proinflammatory and anti-inflammatory cytokines is disturbed, and as in RA, the production of IL-1 and TNF- $\alpha$  is increased.<sup>49,50</sup> This overproduction is significant because both of these cytokines cause the release of other inflammatory cytokines and proteolytic enzymes.

Clinical findings alone show little connection between RA and CD. The immunological and molecular evidence, however, suggest that CD and RA are both I.M.I.D.s. To review, I.M.I.D.s involve an immune response that is inappropriate or excessive and is caused, signified, or accompanied by a dysregulation of the normal cytokine milieu. They also cause acute or chronic inflammatory injury, sometimes severe, in any organ system.

CD likely involves an immune response to a currently unknown gut antigen, which is normally suppressed by appropriate cytokine regulation. Once in place, that aberrant immune response leads to a cytokine-driven inflammatory cascade that eventually causes major tissue damage throughout the gastrointestinal tract and elsewhere in the body. In summary, CD has cytokine dysregulation similar to that found in RA.

**T1DM: The Most Morbid I.M.I.D.** Just as RA has been considered a rheumatological condition and CD a gastrointestinal one, T1DM is typically viewed as an endocrine disease. The reason is obvious: destruction of the pancreas  $\beta$  cells in T1DM produces a hypoinsulinemia that, if untreated, invariably leads to death. The condition's only therapy to date has been insulin replacement, but even with insulin therapy, the risk of morbidity is high. One study showed that after 10 years of routine care, patients with T1DM have a 16% chance of developing sight-threatening retinopathy.<sup>51</sup> The risks of renal failure and lower extremity amputations are also greatly increased in T1DM.<sup>52-54</sup>

Findings of the last decade have established that almost all cases of T1DM have I.M.I.D. pathophysiology.<sup>55-57</sup> It is now thought that Th1 cells mediate the diabetic immune response, and in a T1DM mouse model, suppression of T cell activity prevents development of the disease.<sup>56,58,59</sup> As in the case of RA, the Th1-driven immune response in T1DM generates a series of proinflammatory cytokines, including IL-1, IL-2, IFN- $\gamma$ , and TNF- $\alpha$ .<sup>59</sup> Certain cytokines such as IL-1 are indirectly cytotoxic to the  $\beta$  cells, causing free radicals to be generated that kill the insulin-producing cells.<sup>60</sup> In addition, these proinflammatory cytokines suppress  $\beta$  cell insulin secretion and also stimulate so-called cytotoxic T cells, which then attack and kill the  $\beta$  cells.<sup>59,60</sup> In contrast, the Th2 response and the cytokines that it elaborates have been shown to suppress the development of T1DM, potentially by inhibiting the pathogenic Th1 response, as in the case of IL-4.<sup>57,61</sup>

These findings strongly suggest that, like RA and CD, T1DM is an I.M.I.D. First, it involves an immune response that is excessive and inappropriate: total destruction of the pancreas's insulin-producing  $\beta$  cells. Second, it is caused or signified by a disruption in the normal cytokine milieu, specifically the overproduction of Th1 cytokines.<sup>57</sup> Third, the result of the immune-mediated

**Table 1.** Selected Immune-Mediated Inflammatory Disorders

Condition	Relative Overexpression of Cytokines	Relative Underexpression of Cytokines	Reference
Autoimmune hepatitis	TNF- $\alpha$	IL-2, IL-4	62
Crohn's disease	TNF- $\alpha$ , IL-1, IL-2, IL-6, IL-8, IL-12, and IFN- $\gamma$	IL-3	4, 49, 50
Giant cell arteritis	IFN- $\gamma$ , IL-1, IL-2, TNF- $\gamma$		63, 64
Type 1 diabetes mellitus	TNF- $\alpha$ , IL-1, IL-2, IL-12, IFN- $\gamma$		59, 65
Multiple sclerosis	IL-6, IL-12, TNF- $\alpha$	IL-10	66, 67
Sarcoidosis	TNF- $\alpha$ , IL-1, IL-6, TGF- $\beta$		68, 69
Psoriatic arthritis	TNF- $\alpha$ , IL-1, IL-6, IL-8, IFN- $\gamma$		70
Psoriasis	TNF- $\alpha$		71
Ankylosing spondylitis	TNF- $\alpha$ , IL-10	IFN- $\gamma$ , IL-2	72
Rheumatoid arthritis	TNF- $\alpha$ , IL-1, IL-6		22
Systemic lupus erythematosus	IFN- $\gamma$	TNF- $\alpha$	4
Systemic sclerosis	IL-4, TGF- $\beta$		73, 74
Ulcerative colitis	IL-1, IL-5, IL-6, IL-8, TNF- $\alpha$	IL-3	49, 50, 65

IFN indicates interferon; IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor.

inflammatory destruction of  $\beta$  cells is catastrophic.

**The Other I.M.I.D.s.** Many other autoimmune diseases fit the I.M.I.D. profile, and **Table 1** offers an extensive but by no means complete list. It should be noted that similar cytokine dysregulation can cause different pathologies in different organ systems, depending on when, where, why, and how the dysregulation occurs. This is critical because the most efficacious treatment for apparently unrelated conditions may turn out to be a single drug or group of drugs, as in the case of anti-TNF- $\alpha$  therapy in RA and CD.

Giant cell (or temporal) arteritis and sarcoidosis present interesting examples of similar cytokine dysregulation in different tissue microenvironments causing different clinical findings. The former is an inflammatory condition involving upper extremity and particularly facial arteries, and results in headache, jaw pain, and even blindness, if untreated.<sup>63</sup> In contrast,

sarcoidosis is a systemic inflammatory disorder whose clinical manifestations can range from asymptomatic chest X-ray abnormalities to multiorgan failure.<sup>69</sup>

Despite their clinical dissimilarities, the 2 conditions' cytokine pathophysiology is similar. In sarcoidosis, a condition in which granulomas are formed inappropriately and in absence of an infectious threat, high expression of IL-1 and TNF- $\alpha$  correlates with granuloma formation.<sup>68,75</sup> With giant cell arteritis, there are similar reports of cytokine elevation, specifically of IL-1 and TNF- $\alpha$ .<sup>64,76</sup>

Twenty years from now, a complete list of I.M.I.D.s may encompass not only the relatively rare diseases that we today consider to be of autoimmune origin but other, more prevalent conditions, including chronic obstructive pulmonary disease, asthma, and even atherosclerosis. Not all of these conditions will necessarily be treated or cured with pro- or anticytokine therapy. Cytokine dysregulation and immune-mediated inflammation,

however, may prove to be key drivers of these conditions' pathophysiologies.

### **The Clinical and Economic Burden of I.M.I.D.s for Large Employers and Managed Care Organizations**

Although I.M.I.D.s may affect as much as 5% to 7% of the overall population and can cause severe morbidity and mortality, employers, managed care organizations (MCOs), and benefits consultants have not typically thought of I.M.I.D.s as a specific class of disease<sup>1,4</sup> (personal communication, P. Lopatka, July 2002). Major diagnostic categories (MDCs) group related diseases according to their *International Classification of Diseases, Ninth Revision* (ICD-9) codes, and there is an MDC called Endocrine, Metabolic, and Immunity Disorders.<sup>77</sup> The immunity disorders included in that MDC, however, typically involve reduction, not dysregulation, of immune function (eg, hypogammaglobulinemia).

Rather than being included in that MDC, most I.M.I.D.s fall into MDCs specific to the organs they affect. For example, RA falls into Diseases of the Musculoskeletal System and Connective Tissue, and multiple sclerosis is grouped with Diseases of the Nervous System and Sense Organs.<sup>77</sup> This type of organ-based classification somewhat mirrors the allocation of I.M.I.D.s to medical specialists. Although it is true that rheumatologists treat several kinds of I.M.I.D.s, including RA, systemic lupus erythematosus, and systemic sclerosis, many other I.M.I.D.s are treated by clinicians who specialize in the organs the I.M.I.D.s afflict.

Discussing the reasons why organ-based classification of the I.M.I.D.s still exists is beyond the scope of this review. It should be emphasized, however, that because I.M.I.D.s are usually not seen as a distinct disease class, their aggregate clinical and economic tolls are easily overlooked. Within the epidemiological literature, there are some estimates of the I.M.I.D.s' burden on the overall population, and the article will review those data. Yet for reasons described below, those data may not be relevant to MCOs, large

employers, and benefits consultants. To understand the effect of I.M.I.D.s on the lives most pertinent to these groups, we will also examine I.M.I.D. claim prevalence and cost in a random sample of corporate workers and their dependents. To do so we will use the Medstat Group's MarketScan claims database.

***I.M.I.D. Epidemiology and Cost in the Overall US Population.*** If autoimmune disease affects 5%-7% of Western populations, the prevalence of I.M.I.D.s at this time may be less, as cytokine dysregulation has not been convincingly implicated in all autoimmune conditions. Nevertheless, because autoimmune diseases involve immune-mediated inflammation—which almost by definition involves cytokine dysregulation—it can be argued that many additional autoimmune diseases will be classified as I.M.I.D.s once their molecular mechanisms are fully understood.

**Table 2** lists the prevalence numbers for various I.M.I.D.s as cited in the literature. The prevalence rates vary dramatically, from a low of 16.9 per 100 000 for autoimmune hepatitis to 860 per 100 000 for RA. Although some I.M.I.D.s, such as CD, ulcerative colitis, and T1DM, have similar prevalence among men and women, many I.M.I.D.s, including RA, multiple sclerosis, and systemic lupus erythematosus, are much more prevalent among women.<sup>78</sup> There are at least 2 theories for the differential prevalence. First, female sex hormones may drive immune-mediated inflammation, and second, fetal cells may lodge within the organs of pregnant women during gestation (a phenomenon called microchimerism) and later cause I.M.I.D. pathophysiology.<sup>79-81</sup>

The I.M.I.D. costs reported in the literature similarly vary, both between different I.M.I.D.s and within the range of values for individual I.M.I.D.s. The latter variance results in part from conflicting methodologies used in the different studies to calculate cost.

Before considering these numbers, we will review the different types of costs. Direct costs are those generated in the

provision of care, and indirect costs are those nonmedical losses, such as lost productivity, that result from illness. Intangible costs are those losses, (eg, pain and suffering) that can be measured only subjectively. Direct costs can be divided into those that are medical (eg, surgeon's fees) and nonmedical (eg, parking at the hospital).<sup>95</sup>

Direct medical costs are the expenses most frequently considered in health economic studies, and those are the costs presented here, both from the literature and from MarketScan.<sup>95</sup> When only direct costs are considered, however, the true financial burden of a disease on patients, payers, employers, and society will likely be underestimated. This is especially true with the I.M.I.D.s because so many of them strike young people at the prime of their productivity and subject them to chronic disability.

Of all I.M.I.D.s, RA offers the most extensive direct cost information. Inflated by the Medical Care consumer price index to year 2000 dollars, annual direct costs for the disease range from \$2607 to \$9644<sup>96,97</sup> (Table 3). For the other I.M.I.D.s, annual direct cost estimates range widely, from \$791 for psoriasis to \$15 733 for systemic lupus erythematosus. Most I.M.I.D.s, especially those that are debilitating, exhibit substantial cost skewness (ie, their costs are not evenly distributed among the patients suffering from the disease). With RA, for example, less than 25% of the patient population is responsible for between 43% and 75% of the disease's annual direct cost.<sup>96</sup> With CD and ulcerative colitis, the skewness is even more dramatic, with 2% of the patient population accounting for 34% and 39% of medical costs paid, respectively.<sup>83</sup> If the disease burden of these mostly severely afflicted individuals could be reduced, substantial cost savings might result.

**Table 2.** Prevalence of Immune-Mediated Inflammatory Disorders as Reported in the Literature

Condition	Prevalence		Reference
	Per 100 000	% Female	
Autoimmune hepatitis	16.9	N/A	82
Crohn's disease	1.2-106	~50	83, 84, 85
Giant cell arteritis	27.9	N/A	86
Type 1 diabetes mellitus	192	47.8	78
Multiple sclerosis	120.5	64.2	87
Sarcoidosis	0.2-64	57.3	88
Psoriasis	537	N/A	89
Psoriatic arthritis*	101	N/A	90
Ankylosing spondylitis	100-200	~30	91, 92
Rheumatoid arthritis	860	74.8	78
Systemic lupus erythematosus	50.8	88.2	78, 93
Systemic sclerosis	37.5	92.2	78, 94
Ulcerative colitis	39-117	~50	83,84,85
<b>All Prevalence-Listed I.M.I.D.s†</b>	<b>2258 per 100 000</b>		

\*Psoriatic arthritis prevalence is assumed to be captured within psoriasis prevalence.

†Range midpoints were used for total prevalence calculations.

I.M.I.D. indicates immune-mediated inflammatory disorder; NA, not available.

***I.M.I.D. Epidemiology and Cost in the Medstat MarketScan Population.***

There are 2 main reasons why the above data may not be relevant for MCOs, large employers, and benefits consultants. First, many of these cost and prevalence values are taken from the American population as a whole rather than from the population of workers/dependents to which large employers provide health insurance, and these 2 populations may not be comparable. For example, the overall population might include the sickest I.M.I.D. patients who have become so disabled that they are unable to work, causing the overall population's I.M.I.D. cost-severity mix to be higher than that of the large employer population. In contrast, I.M.I.D. prevalence might be higher in the large employer population than generally if I.M.I.D. patients or caregivers strive to work for large employers, knowing that health insurance and disability benefits are likely to be generous at those corporations.

Second, there is no consensus on how direct cost is calculated in the literature.

Are copayments included or not? Do medical costs reflect what providers charge or what they actually collect? The claims that providers make to payers (ie, charges) represent the price of the providers' services, but not necessarily the actual economic inputs required to offer those services. Alternatively, the amount actually paid to providers for care may be less than its true economic cost. Even if payment equals cost, it may be difficult to define what has been paid where. To make the data even more problematic, most of the literature cost studies were completed before the advent of anticytokine therapy.

Because of these potentially insoluble problems, large employers, MCOs, and benefits consultants need a different approach to understand the prevalence and cost of I.M.I.D.s in the corporate populations they represent. To that end, we calculate prevalence and cost using a method based on what employers designate as "eligible" (to be paid) claims for all inpatient and outpatient I.M.I.D. care. Rather than use a single employer or MCO, we use a group of employers, specifically those that are represented in the Medstat MarketScan database.

### Methods of Analysis

The Medstat Group, a subsidiary of the Thomson Corporation, is a health information company that maintains a multi-source database of privately insured claim and encounter data known as MarketScan. The database includes 4 years of data (1997-2000), approximately 45 companies for each year of data, and approximately 2.5 million covered lives in each year. Individuals can be tracked via a unique identifier through all years for which MarketScan has data, and claims data capture inpatient admissions and services, outpatient services, and drug information. Patients are grouped by age, gender, employee classification, industry of employer, region, and insurance plan type.

Data runs were performed for 1999 and 2000. To calculate the prevalence numbers, the number of unique lives with at least 1 inpatient or outpatient claim indexed to 1 of the ICD-9 codes listed was

**Table 3.** Immune-Mediated Inflammatory Disorder Costs in the United States as Reported in the Literature

Disease	Direct Cost (Year 2000 \$)	Reference
Ankylosing spondylitis	1838	91
Autoimmune hepatitis	N/A	
Crohn's disease	14 647	98
	14 302	83, 99
	5082	100
Type 1 diabetes mellitus	8800	101
Giant cell arteritis	N/A	
Multiple sclerosis	10 732	102
Psoriasis	791	89
Rheumatoid arthritis	9644	103
	9134	103
	7904	103
	7539	103
	6807	104
	6547	96
	6189	105
	5383	106
Sarcoidosis	4765	103
	2971	107
	2882	103
	2621	103
	2607	103
Systemic lupus erythematosus	N/A	
Systemic sclerosis	15 733	108
	8002	109
Ulcerative colitis	5856	94
	9609	83, 99

NA indicates not available.

summed in each plan year. Patient identification numbers were checked between the inpatient and outpatient claims lists to ensure there was no duplication. (Although it is possible that those patients suffering from milder I.M.I.D. cases might not make a single I.M.I.D.-related claim during a plan year, this was deemed to be unlikely. Nevertheless, it should be noted that for this reason, our methodology of prevalence calculation may slightly underestimate true I.M.I.D. prevalence.) The numbers of claimants for each

**Table 4.** Immune-Mediated Inflammatory Disorder Prevalence According to Medstat MarketScan, 1999-2000

Condition	Prevalence Per 100 000	% Female
Autoimmune hepatitis	15.2	48.2
Crohn's disease	118.6	54.9
Type 1 diabetes mellitus	700.3	49.5
Giant cell arteritis	9.5	72.2
Multiple sclerosis	130.4	74.3
Sarcoidosis	61.0	62.5
Psoriasis	329.5	50.8
Psoriatic arthritis	23.6*	48.1
Ankylosing spondylitis	24.2	36.1
Rheumatoid arthritis	335.8	73.7
Systemic lupus erythematosus	97.0	89.4
Systemic sclerosis	18.9	85.3
Ulcerative colitis	156.0	52.9
<b>Sum prevalence of listed I.M.I.D.s</b>	<b>2020 per 100 000</b>	

\*Psoriatic arthritis prevalence is assumed to be captured within psoriasis prevalence  
 I.M.I.D. indicates immune-mediated inflammatory disorder.

I.M.I.D. ICD-9 codes were then divided by the total number of database participants to obtain prevalence rates per 100 000 lives. In addition, male and female distributions were determined. These operations were performed for both 1999 and 2000.

To generate I.M.I.D. cost data, we used the MarketScan's eligible claims field. For those male and female claimants for each ICD-9 codes, we summed all of their eligible claims. This calculation provided the total eligible healthcare claims for those people with I.M.I.D.s. For the people with each I.M.I.D., we then divided their total costs by the number of claimants to generate an average eligible claim cost for each I.M.I.D. patient; this operation was performed separately for both the male and female populations. Next, average eligible claim cost was generated for the overall MarketScan male and female populations, excluding those people with I.M.I.D. claims. Next, that value was subtracted from the average eligible claim

cost for those patients with each I.M.I.D. In this way we removed what we estimated to be the medical cost for I.M.I.D. patients not associated with or secondary to I.M.I.D.s. In essence, the remaining value is the best possible valuation of medical claims directly or indirectly due to I.M.I.D. pathophysiology.

To generate the PMPY figure for each I.M.I.D., we multiplied the prevalence numbers per 100 000 lives by the average I.M.I.D. eligible claims cost (net of the baseline claims cost, as described above) and divided by 100 000. A query established that no claimant fell into multiple claims categories (eg, no patient with T1DM claims also had claims for CD). As a result, the PMPY figures generated are additive.

I.M.I.D. prevalence and gender distribution for the MarketScan population, averaged for the years 1999 and 2000, are listed in Table 4. The percentage-female values from MarketScan are similar to those found in the literature. For example, 49.5% of T1DM claimants in MarketScan are female, as compared to 47.8% in the literature. Likewise, the gender distribution for CD and ulcerative colitis is evenly split both in the literature and in MarketScan. For I.M.I.D.s that are typically more prevalent in the female population, there is also concurrence between MarketScan and the literature. The literature cites female percentages of 74.8% for RA and 88.2% for systemic lupus erythematosus, and from MarketScan the respective numbers are 73.7% and 89.4%.

There are, however, significant differences in the I.M.I.D. prevalence rates between the literature and MarketScan. In several cases, MarketScan I.M.I.D. prevalences are higher than those cited in the literature. For example, the MarketScan prevalences for CD, T1DM, and systemic lupus erythematosus are greater than the literature values by approximately 200% or more. In contrast, the MarketScan prevalence for RA is considerably less than that cited in the literature. Given the evidence that RA incidence has been progressively decreasing for at least 50 years, from 61.2 per 100 000 in 1955-

1964 to 32.7 per 100 000 in 1985-1994, the MarketScan figure may be more reflective of actual RA prevalence.<sup>110,111</sup>

As stated above, one might expect that I.M.I.D. prevalence would be lower in the MarketScan population than in the general population, as most of the I.M.I.D.s are chronic and many can be debilitating. For that reason, people with severe cases might be expected to quit their jobs and apply for Medicare/Social Security Insurance disability payments, thus exiting the MarketScan population. Large employers, however, typically provide benefits for employees and dependents with chronic illnesses that are better than those offered by Medicare.<sup>112</sup> The generosity of these benefits, combined with the disability coverage provided by large employers, might induce employees diagnosed with I.M.I.D.s to stay with their companies for as long as possible. Similarly, healthy workers with I.M.I.D.-afflicted dependents might be compelled to remain with their employers. Moreover, job seekers either suffering from I.M.I.D.s or with dependents who have the diseases might opt for employment at large corporations, especially given the limitations on pre-existing condition exclusions in effect since adoption of the Health Insurance Portability and Accountability Act. For these same reasons, it could be argued that I.M.I.D. patients in MarketScan might be more severely afflicted and thus more costly than those in the general population.

In fact, I.M.I.D. cost estimates are relatively similar in MarketScan and in the literature (Table 5). For example, MarketScan's average, annual, per patient eligible claims for RA are approximately \$6204, as compared to literature citations of \$2607 to \$9694. For CD, the per patient eligible claims are \$7420, as compared to literature reports of \$5082 to \$14 647.

Combining the prevalence and cost data from MarketScan offers perhaps the most important I.M.I.D. cost statistic for large employers, MCOs, and benefits consultants: PMPY eligible claims (Table 6). For each I.M.I.D., the PMPY cost represents the potential amount of disease-related cost divided by the total number of all workers

**Table 5.** Immune-Mediated Inflammatory Disorder Eligible Claim Cost According to Medstat MarketScan, 1999-2000

Condition	Eligible Claim Cost (\$)
Autoimmune hepatitis	5151
Crohn's disease	7420
Type 1 diabetes mellitus	9476
Giant cell arteritis	8642
Multiple sclerosis	9382
Sarcoidosis	5388
Psoriasis	2126
Psoriatic arthritis	3638
Ankylosing spondylitis	4571
Rheumatoid arthritis	6204
Systemic lupus erythematosus	8141
Systemic sclerosis	9075
Ulcerative colitis	5775

and dependents in the insured population. Importantly, PMPY eligible claims reflect the average liability that employers can expect from I.M.I.D.s for claimants who have no other insurance policy primary to their employer-sponsored plan.

Although some PMPY values listed seem small and potentially insignificant (eg, those for autoimmune hepatitis and giant cell arteritis), the sum PMPY expenses for the I.M.I.D.s listed total \$139.84. To put this in perspective, the average per capita non-I.M.I.D. eligible claims cost—which represents the sum of all claims for those people without an I.M.I.D. diagnosis—averaged \$2098.62 in 1999-2000. The per-capita eligible claim costs for the I.M.I.D.s listed are therefore 6.7% of the total per capita claim costs for non-I.M.I.D. patients in MarketScan.

It should be emphasized that many classical autoimmune diseases, such as thyroiditis, autoimmune anemia, and myasthenia gravis, have not been included in the review because the role of cytokines in these conditions has yet to be elucidated. As the frontiers of molecular medicine expand, many of these autoimmune condi-

**Table 6.** Immune-Mediated Inflammatory Disorder Per Member Per Year Costs in Medstat MarketScan, 1999-2000

Condition	PMPY Eligible Claim Cost (\$)
Type 1 diabetes mellitus	66.35
Rheumatoid arthritis	20.84
Multiple sclerosis	12.23
Ulcerative colitis	9.01
Crohn's disease	8.80
Systemic lupus erythematosus	7.90
Psoriasis	7.00
Sarcoidosis	3.29
Systemic sclerosis	1.71
Ankylosing spondylitis	1.11
Giant cell arteritis	0.82
Autoimmune hepatitis	0.78
<b>Total</b>	<b>139.84</b>

PMPY indicates per member per year.

tions may be determined to be cytokine driven, potentially allowing their inclusion in the I.M.I.D. group. For that reason, future studies could show that I.M.I.D.s represent a far greater share of large employers' total healthcare liability.

#### **What Can Be Done—I.M.I.D. Therapy in the 21st Century**

Before the 1940s, little could be done to treat most I.M.I.D.s. That changed in 1948 when American rheumatologist Phillip Hench administered a newly isolated compound called cortisone to patients with RA.<sup>113</sup> In many patients the results of treatment were dramatic, and word spread globally of a new miracle cure, with Hench and his colleagues winning the Nobel Prize for Medicine in 1950.<sup>114</sup> Unfortunately, the severe side effects of cortisone and other glucocorticoid compounds quickly became apparent. In addition, even with therapy, the

disease often seemed to progress, despite the extremely high doses that were used in the early years of treatment.<sup>114</sup>

For other I.M.I.D.s, glucocorticoid therapy has achieved a much less controversial record and is often the standard of care. In CD, for example, prednisone is widely used for flares, and methylprednisone is standard therapy for multiple sclerosis relapses.<sup>115,116</sup> Nevertheless, even with the much lower doses used now than in Hench's time and careful tapers, prolonged glucocorticoid therapy remains fraught with side effects, including but not limited to osteoporosis, hypertension, hyperglycemia, and weight gain.<sup>117</sup> Cognizant of these side effects, clinicians have long wanted a new type of I.M.I.D. therapy with the same wide-reaching applicability and efficacy as glucocorticoids but with much greater safety.

Over the years, a wide range of immunosuppressant therapies, including azathioprine, cyclophosphamide, cyclosporine, leflunomide, methotrexate, and tacrolimus, have been used to treat I.M.I.D.s, often with great success.<sup>118</sup> Yet because many of these therapies involve serious systemic toxicity, the search continued for an effective I.M.I.D. therapy with moderate side effects.

The concept that proinflammatory cytokines might play a key role in the pathogenesis of not one but many I.M.I.D.s led investigators to theorize that blocking those cytokines might have therapeutic benefit. The hypothesis was correct, and currently, at least 5 anticytokine therapies have significantly advanced the treatment of several I.M.I.D.s, including RA and CD. In this section the review will examine the anticytokine therapies currently in use and those in development. *It is important to emphasize that anticytokine therapy is not appropriate for all patients with all I.M.I.D.s.* Nevertheless, the data presented below demonstrate the potential for significant therapeutic benefit in certain clinical situations.

**TNF- $\alpha$  Blockade—The First Anticytokine Therapy.** As mentioned above, several mouse studies suggested that TNF- $\alpha$

blockade could be therapeutic in reducing the joint inflammation of RA.<sup>35,119</sup> These findings, as well as an overall appreciation of the inflammatory capabilities of TNF- $\alpha$ , presaged the development of several different TNF- $\alpha$ -blocking molecules, 2 of which are now available commercially. Anti-TNF- $\alpha$  therapy is not appropriate for all I.M.I.D. patients, but for certain patients there is substantial evidence of clinical benefit.

**Infliximab.** Infliximab, a mouse-human chimeric antibody against TNF- $\alpha$ , showed promise in early human clinical trials for RA. It significantly reduced a host of inflammatory signs, including joint swelling.<sup>120</sup> A larger trial tested infliximab with and without methotrexate, a standard therapy for RA. This trial of 101 patients showed that infliximab infusions of 10 mg/kg combined with methotrexate caused a 70%-90% reduction in the number of swollen joints and C-reactive protein, a marker for inflammation.<sup>121</sup> The efficacy of infliximab, however, was most convincingly demonstrated in the randomized, controlled Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT). Four hundred and twenty-eight patients receiving methotrexate were given infliximab, 3 mg/kg or 10 mg/kg, or placebo for 2 years. Infliximab and methotrexate were shown to be significantly better than methotrexate alone in reducing the signs and symptoms of RA. Most important, infliximab and methotrexate—but not methotrexate alone—were shown to halt the progression of joint damage.<sup>122</sup>

Infliximab's therapeutic value is not limited to RA—not surprising given the common cytokine-driven pathophysiology of many I.M.I.D.s. Infliximab, for example, has proven both safe and efficacious in the treatment of CD. An initial clinical trial of 108 patients showed that a single infusion of infliximab was an effective short-term treatment in patients with moderate-to-severe disease, with 33% of infliximab patients but only 4% of placebo controls achieving remission.<sup>123</sup> A subsequent study showed that infliximab enabled

patients to attain remission and that repeated infliximab infusions could help recipients maintain it.<sup>124</sup>

Infliximab's use has not been limited to RA and CD. Open-label studies have shown it to be effective in the treatment of psoriasis and ankylosing spondylitis, and case reports have demonstrated its therapeutic value in sarcoidosis and giant cell arteritis.<sup>71,125-127</sup>

**Etanercept.** A fusion protein containing domains from the TNF- $\alpha$  receptor, etanercept is the other commercially available anti-TNF- $\alpha$  therapy.<sup>3</sup> A blinded trial of 180 RA patients showed those receiving etanercept had a 61% reduction in their number of swollen joints, as compared to a 25% reduction with placebo.<sup>128</sup> In a subsequent study in which RA patients received etanercept and methotrexate or methotrexate alone, 39% of the etanercept patients met ACR 50 criteria, as compared to 3% of those patients receiving methotrexate alone.<sup>129</sup> (The American College of Rheumatology [ACR] definition of improvement in clinical trials involves a) improvement in joint counts and b) improvement in at least 3 of the following: patient assessment, physician assessment, erythrocyte sedimentation rate, pain scale, and functional questionnaire. The ACR 20, ACR 50, and ACR 70 criteria reflect an improvement of 20%, 50%, or 70% in these metrics).<sup>130</sup> Etanercept has also been shown to be effective in reducing the signs and symptoms of juvenile RA.<sup>131</sup>

Like infliximab, etanercept has demonstrated efficacy in treating other I.M.I.D.s besides RA. A randomized, controlled trial of 60 patients with psoriasis and psoriatic arthritis showed that etanercept-treated patients achieved a 46% improvement in their psoriasis symptoms, as compared to a 9% improvement for placebo-treated patients.<sup>132</sup> In addition, 87% of etanercept-treated patients had significant improvement of their arthritic symptoms, as compared to 23% of patients treated with placebo.<sup>132</sup> A trial of 40 patients has demonstrated etanercept to be effective in the treatment of ankylosing spondylitis,

with 80% of patients in the treatment group achieving a clinical response as compared to 30% of patients in the placebo group.<sup>133</sup>

***IL-1 and IL-2 Blockade—Another Anti-inflammatory Strategy.*** The above-mentioned studies confirmed what has long been suspected about TNF- $\alpha$ : it plays a proinflammatory role in several I.M.I.D.s. Similarly, a recently approved anti-IL-1 therapy, anakinra, and 2 recently approved anti-IL-2 therapies, daclizumab and basiliximab, highlight the importance of these 2 cytokines in the generation of I.M.I.D. pathophysiology.

Approved in 2001, anakinra is the recombinant version of a naturally occurring molecule known as the IL-1 receptor antagonist.<sup>134</sup> IL-1 plays a critical role in the inflammatory cascade of RA, and by blocking IL-1, anakinra has demonstrated clinical efficacy in the treatment of the disease.<sup>135</sup> In a randomized, controlled trial of 472 patients, 43% of those receiving anakinra at 150mg/day achieved the ACR 20 response, as compared to 27% of patients receiving placebo.<sup>134</sup>

Like IL-1, IL-2 plays a key part in T cell activation, an important event in the inflammatory process that leads to rejection of organ transplants in the absence of immunosuppressive therapy. By blocking IL-2, both daclizumab and basiliximab have been shown to reduce the rejection of kidney transplants at 6 months as compared to placebo, by 37% and 32%, respectively.<sup>136,137</sup> Given the widespread role of IL-2 in the inflammatory process, IL-2 blockade may prove to have wide-reaching therapeutic utility.

***Anticytokine Therapy—Is it a Panacea?*** The new anticytokine therapies have dramatically improved the prognoses for several I.M.I.D.s, including RA and CD. The success of these therapies, however, raises the question of whether blocking cytokine activity might interfere with normal physiology. Unfortunately, anticytokine therapies may, in relatively rare instances, have

that effect.<sup>138</sup> Both infliximab and etanercept have been associated anecdotally with systemic lupus erythematosus and more broadly with the induction of anti-nuclear antibodies in as many as 10% of treated patients.<sup>139,140</sup>

There is also evidence that inhibition of TNF- $\alpha$  may suppress normal immunity. For example, a retrospective study of 147 000 patients treated with infliximab suggests the rate of active tuberculosis infection is higher in those patients than in controls.<sup>141</sup> Similarly, a series of randomized, controlled trials with 771 patients showed those receiving infliximab had a 26% risk of any infection during 27 weeks of follow-up as compared to a 16% risk at 20 weeks for those receiving placebo. Despite this increased risk of infections in the infliximab population, there was no increased risk of serious infection.<sup>142</sup> In summary, none of the anticytokine therapies are without side effects, but these adverse events appear to be relatively rare.<sup>142,143</sup>

***Anticytokine Therapy—The Next Generation.*** With the success of infliximab and etanercept, many new anticytokine therapies are in development, and several are in phase III trials. Like infliximab, many of these products are monoclonal antibodies. Because monoclonal antibodies in phase III trials have a 30% or higher chance of receiving final Food and Drug Administration approval, large employers, MCOs, and benefit consultants should consider these molecules in advance of their potential launches.<sup>144</sup>

Adalimumab, a human anti-TNF monoclonal antibody; CDP571, a “humanized” anti-TNF monoclonal antibody; and CDP870, a high affinity anti-TNF- $\alpha$  antibody fragment are each in phase III clinical trials.<sup>145-147</sup> Preliminary results from the Safety Trial of Adalimumab in Rheumatoid Arthritis (STAR) indicate a 30% achievement of ACR 50 criteria with adalimumab treatment, as compared to 11% with placebo.<sup>148</sup> With the success of anti-TNF- $\alpha$  therapy in the treatment of CD, trials of adalimumab for that condition are also scheduled.<sup>149</sup>

A phase III trial of CDP571 for CD has recently yielded preliminary results, which showed treated patients did not meet the study's primary end point.<sup>147</sup> The drug has, however, shown promise as a potential therapy for RA.<sup>150</sup> CDP870 is also undergoing phase III testing for RA and CD.<sup>145</sup> CDP870 is different from adalimumab and CDP571, however, in that it is PEGylated (ie, the drug formulation contains a polyethylene glycol [PEG] moiety that improves the drug's pharmacokinetics and allows it to stay in the circulation longer).<sup>151,152</sup> The PEGylation strategy is also being used with a new soluble version of the TNF- $\alpha$  receptor, currently in phase II trials.<sup>153</sup> In addition to these anti-TNF- $\alpha$  therapies, several molecules targeting other cytokines are also in development (Table 7).

### Conclusion

I.M.I.D.s result from inappropriate or excessive immune responses. I.M.I.D.s are caused, signified, or accompanied by dysregulation of the normal cytokine milieu, and they lead to acute or chronic inflammatory injury that may be life-threatening. Healthcare stakeholders have been slow to embrace the I.M.I.D. concept, but the past decade's advances in molecular medicine have shown that many ostensibly unrelated diseases, including RA, CD, and T1DM, share I.M.I.D. pathophysiology. That anticytokine therapies have been effective in treating a number of I.M.I.D.s further emphasizes the legitimacy of the I.M.I.D. concept. For large employers, I.M.I.D.s represent more than 6% of total healthcare spending, and that number will likely grow as many diseases not currently classified as I.M.I.D.s are shown to share that pathophysiology. As a result, it becomes ever more critical that providers, payers, large employers, and benefits consultants understand the clinical and economic burden of I.M.I.D.s. Without that understanding, they risk underestimating what may be a key cost driver—both economically and clinically—for years to come.

**Table 7.** Other Anticytokine Therapies in Development

Condition	Product	Cytokine Targeted	Development Phase of Product
Crohn's disease	J-695	IL-12	Phase II
	SMART	IFN- $\gamma$	Phase II
Multiple sclerosis	J-695	IL-12	Phase II
Rheumatoid arthritis	J-695	IL-12	Phase II
	HuMax-IL15	IL-15	Phase II
Psoriasis	ABX-IL-8	IL-8	Phase II
Systemic sclerosis	CAT-192	TGF- $\beta$	Phase II

IFN indicates interferon; IL, interleukin; TGF, transforming growth factor.

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