Review

Cytokines and anti-cytokines as therapeutics — An update

Vandana Tayal *, Bhupinder Singh Kalra

Department of Pharmacology, Maulana Azad Medical College, New Delhi, 110002, India

Received 15 May 2007; received in revised form 12 October 2007; accepted 18 October 2007

Available online 25 October 2007

Abstract

Cytokines which comprise of a family of proteins — interleukins, lymphokines, monokines, interferons, and chemokines, are important components of the immune system. They act in concert with specific cytokine inhibitors and soluble cytokine receptors to regulate the human immune response. Their physiologic role in inflammation and pathologic role in systemic inflammatory states are now well recognized. An imbalance in cytokine production or cytokine receptor expression and/or dysregulation of a cytokine process contributes to various pathological disorders. Research is progressing rapidly in the area of cytokines and their therapeutic targets, the two major therapeutic modalities being the administration of purified recombinant cytokines and the use of their antagonists in various inflammatory disorders. However, given the large number of cytokines, it is disappointing that only relatively few can be used clinically. In the present article, we have made an attempt to review and present a glimpse of the history as well as up to date information that is pertinent to cytokines and anti-cytokine therapies in the treatment of cancer, autoimmune disorders and various other related diseases.

© 2007 Elsevier B.V. All rights reserved.

Keywords: Interferons; Interleukins; Tumor necrosis factor

Contents

1. Introduction ...............................................................2
2. History ..................................................................2
3. Properties of cytokines ..........................................................2
4. Cytokines as therapeutic agents .....................................................3
  4.1. Interferons ...................................................................3
  4.2. Interferon-alpha .............................................................3
    4.2.1. IFN-α-2a and IFN-α-2b .................................................3
    4.2.2. Peginterferon-alpha ....................................................4
    4.2.3. IFN-α con-1 .......................................................4
    4.2.4. Interferon-α-n3 .....................................................4
  4.3. Adverse effects of interferon-alpha ................................................6
  4.4. Interferon-beta ...........................................................6
    4.4.1. Interferon-β-1a and interferon-β-1b ......................................6
  4.5. Interferon-gamma .........................................................6
    4.5.1. Interferon-gamma-1b ...................................................6
  4.6. Interleukin-2 (IL-2, aldesleukin) ..................................................7
5. Anti-cytokines as therapeutic agents ...................................................7
  5.1. Tumor necrosis factor alpha inhibitors ................................................7
    5.1.1. Indications ..............................................................8

* Corresponding author. B-21, Tarang Apartments, 19-I.P Extension, New Delhi, 110092, India. Tel.: +91 11 9899027018.
E-mail address: vandana_muskan@rediffmail.com (V. Tayal).

0014-2999/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2007.10.049
1. Introduction

Cytokine is a word that comes from cyto meaning “cell” and kinin meaning ‘hormones’. Cytokines are soluble hormone-like proteins that allow for communication between cells and the external environment. It is an umbrella term which encompasses lymphokines, monokines, interleukins, colony stimulating factors (CSFs), interferons (IFNs), tumor necrosis factor (TNF) and chemokines (Leonard, 1999).

Cytokines are secreted by white blood cells as well as variety of other cells (fibroblasts, endothelial cells, epithelial cells, etc.) in the body in response to inducing stimuli, and are not constitutively expressed. It was in fact based on the realization that cells other than those of the immune system also secrete biologically active substances, that the concept of cytokines was proposed. It was Stanley Cohen in 1974 who for the first time introduced the term “cytokine” (Cohen et al., 1974, 2004).

Cytokines serve many functions in the body such as mediating and regulating immunity, inflammation and hematopoiesis, but the largest group of cytokines is involved in immune cell proliferation and differentiation (Table 1). Although cytokines are produced by many cell populations, the predominant producers are helper T-cells (Th) and macrophages.

2. History

The research in the field of cytokines began as early as in the 1950s with the identification of some of the factors like ‘endogenous pyrogen’ [now also known as interleukin-1 (IL-1)] (Bennett and Beeson, 1953), nerve growth factor (Levi-Montalcini and Hamburger, 1953) and interferon (Isaacs and Lindenmann, 1957).

In 1957, Alick Isaacs and Jean Lindenmann identified interferon-α as a factor produced upon stimulation of cells by viruses and which had the ability to protect cells from infection with viruses of any kind. In fact, the name ‘interferon’ comes from the ability to interfere with the production of new virus particles. They noted that it made cells resistant to viral infection but exerted no adverse effects on uninfected cells. This observation inspired hopes that IFN could be used to treat viral infections (Isaacs and Lindenmann, 1957).

In 1966, John David and Barry Bloom independently identified ‘migration inhibiting factor’. This factor was found to be released from antigen activated lymphocytes and caused inhibition of the movement of macrophages in vitro (David, 1966; Bloom and Bennett, 1966). Subsequently, immunologists discovered that lymphocytes produce soluble mediators that affect many functions of the immune system. These soluble mediators were collectively termed as ‘lymphokines’ by a scientist ‘Dudley Dumonde’ in 1969 (Dumonde et al., 1969). Similarly, active mediators derived from macrophages and monocytes in culture came to be known as ‘monokines’.

Tumor necrosis factor (TNF), another important factor, was described originally in the 1970s as a mediator of lipopolysaccharide-induced necrosis of transplantable tumors. It was first isolated from the serum of mice treated with bacterial endotoxin, and was shown to replicate the ability of endotoxin to induce hemorrhagic necrosis of sarcomas (Carswell et al., 1975). TNF comprises of a family which primarily includes TNF-α, TNF-β, Fas ligand, TNF-related apoptosis inducing ligand (TRAIL), nerve growth factor, and CD40 ligand (Ksontini et al., 1998).

In the 1980s, colony stimulating factors (CSFs), discovered by Donald Metcalf and colleagues, were found to stimulate growth and differentiation of various elements of bone marrow and were named according to the specific elements they support, like Granulocyte CSF (G-CSF), Granulocyte monocyte CSF (GM-CSF) and Erythropoietin.

In the late 1980s scientists isolated the signaling molecules chemokines, which allowed leukocytes to communicate with one another and seek out and destroy invading pathogens.

Anti-cytokine therapy was pioneered by Simon Skurkovich who detected interferon in the circulation of patients with autoimmune diseases and proposed that neutralization of IFN could be therapeutic (Skurkovich et al., 1974; Skurkovich and Eremkina, 1975; Skurkovich and Skurkovich, 1989). Another milestone of anti-cytokine therapy was the demonstration by Bruce Beutler and colleagues that administration of antibody to TNF protected mice and baboons from bacterial sepsis (Beutler et al., 1985).

Eventually, advances in understanding of the role of cytokines in immune and inflammatory disorders led to the development of cytokine-based therapies.

3. Properties of cytokines

Before we discuss various cytokine-based therapies it is important to become familiar with some basic properties of cytokines.

1. Pleiotropy, i.e. a single cytokine can act on many different types of cells rather than a single cell type. For example IL-2 initially discovered as a T-cell growth factor also affects B-cell and natural killer (NK) cell growth and differentiation.
2. Redundancy, i.e. similar function can be stimulated by different cytokines. For example IL-1 and TNF-α both act as inflammatory mediators.

3. “Multifunctional” refers to the fact that the same cytokine may be able to regulate several different immune functions.

Table 1 shows a list of various cytokines, their source, target site of action and major functions.

### Table 1
Source and physiological role of various cytokines

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Main sources</th>
<th>Target cell</th>
<th>Major function</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>Macrophages, B-cells, dendritic cells</td>
<td>B-cells, NK cells, T-cells</td>
<td>Proliferation and differentiation, pyrogenic, BM cell proliferation</td>
</tr>
<tr>
<td>IL-2</td>
<td>T-cells</td>
<td>Activated T- and B-cells, NK cells</td>
<td>Proliferation and activation</td>
</tr>
<tr>
<td>IL-3</td>
<td>T-cells</td>
<td>Stem cells</td>
<td>Hematopoietic precursor proliferation and differentiation</td>
</tr>
<tr>
<td>IL-4</td>
<td>Th cells</td>
<td>B-cells, T-cells macrophages</td>
<td>Proliferation of B and cytotoxic T-cells, enhances MHC class II expression, stimulates IgG and IgE production</td>
</tr>
<tr>
<td>IL-5</td>
<td>Th cells</td>
<td>Eosinophils, B-cells</td>
<td>Proliferation and maturation, stimulates IgA and IgM production</td>
</tr>
<tr>
<td>IL-6</td>
<td>Th cells, macrophages, fibroblasts</td>
<td>Activated B-cells, plasma cells</td>
<td>Differentiation into plasma cells</td>
</tr>
<tr>
<td>IL-7</td>
<td>BM stromal cells, epithelial cells</td>
<td>Stem cells</td>
<td>B- and T-cell growth factor</td>
</tr>
<tr>
<td>IL-8</td>
<td>Macrophages</td>
<td>Neutrophils</td>
<td>Chemotaxis, pro-inflammatory</td>
</tr>
<tr>
<td>IL-9</td>
<td>T-cell</td>
<td>T-cell</td>
<td>Growth and proliferation</td>
</tr>
<tr>
<td>IL-10</td>
<td>T-cell</td>
<td>B-cells, macrophages</td>
<td>Inhibits cytokine production and mononuclear cell function, anti-inflammatory</td>
</tr>
<tr>
<td>IL-11</td>
<td>BM stromal cells</td>
<td>B-cells</td>
<td>Differentiation, induces acute phase proteins</td>
</tr>
<tr>
<td>IL-12</td>
<td>T-cells</td>
<td>NK cells</td>
<td>Activates NK cells</td>
</tr>
</tbody>
</table>

**Interferons**

<table>
<thead>
<tr>
<th>Interferons</th>
<th>Main sources</th>
<th>Target cell</th>
<th>Major function</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-α</td>
<td>Leukocytes</td>
<td>Various</td>
<td>Anti-viral, anti-proliferative</td>
</tr>
<tr>
<td>IFN-β</td>
<td>Fibroblasts</td>
<td>Various</td>
<td>Anti-viral, anti-proliferative</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>T-cells</td>
<td>Various</td>
<td>Anti-viral, macrophage activation, increases neutrophil and monocyte function, MHC-I and -II expression on cells</td>
</tr>
</tbody>
</table>

**Tumor necrosis factor**

<table>
<thead>
<tr>
<th>Tumor necrosis factor</th>
<th>Main sources</th>
<th>Target cell</th>
<th>Major function</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>Macrophages</td>
<td>Macrophages</td>
<td>Phagocyte cell activation, endotoxic shock</td>
</tr>
<tr>
<td>TNF-β</td>
<td>Monocytes</td>
<td>Tumor cells</td>
<td>Tumor cytotoxicity, cachexia</td>
</tr>
<tr>
<td>TNF-β</td>
<td>T-cells</td>
<td>Phagocytes, tumor cells</td>
<td>Chemotactic, phagocytosis, oncostatic, induces other cytokines</td>
</tr>
</tbody>
</table>

**Colony stimulating factors**

<table>
<thead>
<tr>
<th>Colony stimulating factors</th>
<th>Main sources</th>
<th>Target cell</th>
<th>Major function</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF</td>
<td>Fibroblasts, endothelium</td>
<td>Stem cells in BM</td>
<td>Granulocyte production</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>T-cells, macrophages, fibroblasts</td>
<td>Stem cells</td>
<td>Granulocyte, monocyte, eosinophil production</td>
</tr>
<tr>
<td>M-CSF</td>
<td>Fibroblast, endothelium</td>
<td>Stem cells</td>
<td>Monocyte production and activation</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Endothelium</td>
<td>Stem cells</td>
<td>Red blood cell production</td>
</tr>
</tbody>
</table>

**Others**

<table>
<thead>
<tr>
<th>Others</th>
<th>Main sources</th>
<th>Target cell</th>
<th>Major function</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGF-β</td>
<td>T-cells and B-cells</td>
<td>Activated T- and B-cells</td>
<td>Inhibit T- and B-cell proliferation, inhibit hematopoiesis, promote wound healing</td>
</tr>
<tr>
<td>MIP</td>
<td>Macrophages</td>
<td>T-cells</td>
<td>Chemotaxis</td>
</tr>
</tbody>
</table>

Interferons are generally classified according to their cellular origin and the type of receptors they bind to (Sen and Lengyel, 1992; Jonasch and Haluska, 2001) (Table 1). Type I interferons include over 25 subtypes of interferon-alpha, interferon-beta, interferon-omega, and interferon-tau. There is only one type II interferon, interferon-gamma, which is chemically and pharmacologically distinct from IFN-α and IFN-β. Type I IFNs induce anti-proliferative and anti-viral activity whereas type II IFN, interferon-gamma, has weaker anti-viral activity but more potent immunomodulatory properties, and binds to a completely different receptor than type I IFNs (Sen and Lengyel, 1992; Jonasch and Haluska, 2001).

Interferons exert their effects by binding to membrane receptors, which initiates a series of intracellular signaling events. The activation of Janus activated kinase (JAK)-signal transducers and activators of transcription (STAT) signaling pathway leads to transcriptional activation of genes (O’Shea et al., 2000). The gene products so formed are responsible for the anti-viral, anti-proliferative and immunomodulatory effects of interferons.
Interferons have no direct action on the virus, nor do they inhibit adsorption of virus on the cell. Rather they block viral multiplication by inhibiting transcrip- tive and translational ability of viral nucleic acid.

From the historical viewpoint, IFN was the first cytokine to be purified and produced in the recombinant form for widespread clinical application. Various interferons approved for clinical use include: IFN-α-2a, 2b, pegylated IFN-α-2a, 2b, IFN-α-n3, IFN-α con-1, IFN-β-1a, IFN-β-1b and IFN-γ-1b (Cada et al., 2000). Table 2 shows a list of these interferons with their approved indications and dosage recommendations.

4.2. Interferon-alpha

4.2.1. IFN-α-2a and IFN-α-2b

These are highly purified proteins containing 165 amino acid obtained by recombinant DNA technology using genetically engineered E. coli. However, IFN-α-2b differs from IFN-α-2a by one amino acid i.e. arginine instead of lysine at position 23 (Cada et al., 2000).

Both these IFNs are approved for several conditions like chronic hepatitis C (often in combination with nucleoside analog ribavirin), AIDS-related Kaposi’s sarcoma (Evans et al., 1991), chronic myelogenous leukemia (Enright and McGlave, 1997) and hairy cell leukemia (Romeril et al., 1989). In addition, IFN-α-2b is indicated for the treatment of malignant melanoma (Agarwala and Kirkwood, 1998), condyloma acuminata (Yildirim et al., 2004), follicular lymphoma (Avilés et al., 2004) and chronic hepatitis B (Janssen et al., 1999).

Interferon, whether it is used alone or in combination with ribavirin, is the gold standard treatment for hepatitis C. Several types of interferon-α have been studied and are approved for the treatment of chronic hepatitis C-IFN-α-2a, IFN-α-2b, pegylated IFN-α and IFN-αcon-1.

A meta-analysis of randomized trials using interferon in the treatment of viral hepatitis C in naive patients revealed that only about 17% of patients with chronic hepatitis C obtained a sustained virological response on interferon monotherapy (Thevenot et al., 1999). However combination therapy with IFN and ribavirin permanently eradicated virus in about 40% of patients (McHutchison et al., 1998). Thus, combination therapy has been a major advancement in the treatment of chronic hepatitis C in naive patients, as well as in those who have failed or have relapsed after previous IFN monotherapy (Davis et al., 1998). Recent studies have confirmed that long acting pegylated interferons show better anti-viral responses than standard interferon-alpha preparations (Zeuzem et al., 2000; Lindsay et al., 2001).

4.2.2. Peginterferon-alpha

These are pegylated forms of interferon-alpha. Pegylation involves attaching a large inactive molecule, polyethylene glycol (PEG), to IFN-alpha by a covalent bond which shields the protein from enzymatic degradation. Pegylation offers many advantages over non-pegylated forms of IFN-extended circulating half-life, increased drug stability, enhanced drug solubility and lower toxicity (Glue et al., 2000). Because pegylated products have substantially long half-life (10 times more than IFN-α), it allows once weekly dosing in contrast to thrice weekly dosing with conventional IFN. This results in enhanced patient compliance and clinically superior anti-viral activity. However, the major constraint in their use is high cost (2–3 times) in comparison to non-pegylated IFNs (Glue et al., 2000).

Pegylated interferon in combination with ribavirin is approved for use in patients with chronic hepatitis C and has significantly improved the viral eradication rates (Shepherd et al., 2004; Ferenci, 2006). Published studies have shown that peginterferon-alpha alone results in “sustained response” rates of 30% to almost 40% which increases to over 50% when combined with ribavirin (Zeuzem et al., 2000; Fried et al., 2001). Thus presently the best available treatment for chronic hepatitis C appears to be peginterferon-alpha plus ribavirin. However, the issue regarding patients being unresponsive to even this combination therapy, remains unsolved and needs further research.

Pegylated interferon therapy is in advanced phase of evaluation for treatment of acute hepatitis C infection in HIV-coinfected individuals. (ClinicalTrials.gov Identifier: NCT00132210). Other than hepatitis, peginterferon-alpha is also being evaluated in patients with stage IV melanoma to study its anti-tumor efficacy (ClinicalTrials.gov Identifier: NCT00049530).

4.2.3. IFN-α con-1

IFN-α con-1 also known as consensus interferon is a synthetic recombinant product containing 166 amino acid sequences. It varies from IFN-α-2a and IFN-α-2b by 20 amino acids. These amino acid differences lead to different binding affinities at the cell surface receptors and ultimately differences in potency among these interferons.

IFN-α con-1 is approved for the treatment of chronic hepatitis C viral infection and is the only interferon effective in the treatment of relapsers and non-responders to previous interferon-alpha therapy (Melian and Plosker, 2001). When given alone at a dose of 9 µg three times a week for 24 weeks to treatment naive patients, IFN-α con-1 was found to be safe and effective with overall sustained response in 16% of patients (Kao et al., 2000). Among non-responders, 13% of those who do not respond to an initial course of alpha interferon monotherapy and 58% of those who relapse after initially responding to treatment, experience sustained viral eradication with 15 µg of α con-1 three times a week for 48 weeks (Keeffe and Hollinger, 1997; Melian and Plosker, 2001). Similarly, 40–44% of patients who do not respond to IFN-α-2b and ribavirin therapy respond well to IFN-α con-1 and ribavirin combination.

Current research is now devoted to assess the effectiveness of IFN-α con-1 plus ribavirin in those patients who do not respond to pegylated interferon plus ribavirin combination therapy (ClinicalTrials.gov Identifier: NCT00456248). Promising results from this research will significantly improve the treatment of patients with chronic hepatitis C infection.

4.2.4. Interferon-α-n3

Interferon-α-n3 is a natural, human IFN-α obtained from human leukocytes (induced by murine virus) for clinical use (Jonasch and Haluska, 2001). It is approved for the treatment of refractory condyloma acuminata (CA), which include venereal or genital warts (Jonasch and Haluska, 2001; Table 2). The safety and
<table>
<thead>
<tr>
<th>Generic name</th>
<th>Approved indications</th>
<th>Recommended adult dose</th>
<th>Route of administration</th>
<th>Half-life</th>
<th>Adverse effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-α-2a</td>
<td>Chronic hepatitis C</td>
<td>3 MU three times weekly for 12 months</td>
<td>s.c or i.m</td>
<td>2-5 h</td>
<td>Flu-like syndrome, thrombocytopenia, granulocytopenia, elevation in transaminases, neuropsychiatric symptoms</td>
<td>Romeril et al. (1989), Evans et al. (1991), Enright and McGlave (1997)</td>
</tr>
<tr>
<td></td>
<td>Hairy cell leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic myelogenous leukemia, AIDS-related KS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN-α-2b</td>
<td>Chronic hepatitis B</td>
<td>5 MU OD or 10 MU three times weekly for 16 weeks</td>
<td>s.c, i.v or i.m</td>
<td>2-5 h</td>
<td>Same as with IFN-α-2a</td>
<td>Pol et al. (1999), Romeril et al. (1989), Evans et al. (1991), Enright and McGlave (1997), Yildirim et al. (2004), Neri et al. (2006)</td>
</tr>
<tr>
<td></td>
<td>Chronic hepatitis C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Condyloma acuminata</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follicular lymphoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hairy cell leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AIDS-related KS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malignant melanoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN-α con-1</td>
<td>Chronic hepatitis C</td>
<td>9 μg three times weekly for 24 weeks</td>
<td>s.c</td>
<td>6-10 h</td>
<td>Same as with IFN-α-2a</td>
<td>Condus et al. (1997)</td>
</tr>
<tr>
<td></td>
<td>For relapse or non-responders – 15 μg SC three times weekly for 24 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon-α-nl</td>
<td>Condyloma acuminata</td>
<td>250,000 IU (0.05 mL) per wart, twice weekly for 8 weeks</td>
<td>Intralesional inj</td>
<td>3-8 h</td>
<td>Same as with IFN-α-2a</td>
<td>Friedman-Kien (1995), Friedman-Kien et al. (1988)</td>
</tr>
<tr>
<td>Pegylated IFN-α-2a</td>
<td>Chronic hepatitis C</td>
<td>180 μg once weekly</td>
<td>s.c</td>
<td>80 h</td>
<td>Headache, fatigue, myalgia, injection site reactions</td>
<td>Shepherd et al. (2004), Weinstock-Guttman and Jacobs (2000)</td>
</tr>
<tr>
<td>Pegylated IFN-α-2b</td>
<td>Chronic hepatitis C</td>
<td>40–150 μg once weekly</td>
<td>s.c</td>
<td>40 h</td>
<td>Headache, fatigue, myalgia, injection site reactions</td>
<td>Shepherd et al. (2004), Ferenci (2006)</td>
</tr>
<tr>
<td>IFN-β-1a</td>
<td>Relapsing forms of multiple sclerosis</td>
<td>30 μg once weekly</td>
<td>i.v, i.m or s.c</td>
<td>10 h</td>
<td>Fever, chills, myalgia</td>
<td>Weinstock-Guttman and Jacobs (2000), Ferenci (2006), Paklanian et al. (2006), Ciocco et al. (2006)</td>
</tr>
<tr>
<td>IFN-β-1b</td>
<td>Relapsing forms of multiple sclerosis</td>
<td>8,000,000 IU/inj every 2nd day</td>
<td>i.v or s.c</td>
<td>8 min–4 h</td>
<td>Fever, chills, myalgia</td>
<td>Key et al. (1995), Bemiller et al. (1999)</td>
</tr>
<tr>
<td></td>
<td>Malignant osteopetrosis, Chronic granulomatous disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Body surface area (BSA) &gt; 0.5 m²–50 μg/m² (1 million IU/m²) thrice weekly, if BSA &lt; 0.5 m²–1.5 μg/kg/dose s.c TIW 1–2 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anakinra (hIL-1ra)</td>
<td>Rheumatoid arthritis</td>
<td>600,000 IU/kg every 8 h by a 15-minute IV infusion for a max of 14 doses</td>
<td>i.v</td>
<td>85 min</td>
<td>Capillary leak syndrome (CLS) and flu-like symptoms, low blood pressure, decreased kidney and lung function, respiratory distress, cardiac abnormalities, changes in mental status</td>
<td>Schmidinger et al. (2004), Atkins et al. (1999)</td>
</tr>
<tr>
<td>Aldesleukin (IL-2)</td>
<td>Metastatic renal cell cancer, metastatic melanoma</td>
<td></td>
<td>i.v</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Prophylaxis of acute organ rejection in renal transplant patients</td>
<td>2 doses of 20 mg by i.v infusion, one 2 h prior to transplant and the second 4 days after transplant</td>
<td>i.v</td>
<td>7 days</td>
<td>Nausea, constipation, pain, urinary tract infection, upper respiratory</td>
<td>Gelder et al. (2004), Ramirez and Marino (2007), Chapman and Keating (2003)</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Prophylaxis of acute organ rejection in renal transplant patients</td>
<td>1 mg/kg given 24 h prior to transplant followed by 4 doses at 14 day intervals (2, 4, 6 and 8 weeks)</td>
<td>i.v</td>
<td>20 days</td>
<td>Nausea, constipation, headache</td>
<td>Gelder et al. (2004), Chapman and Keating (2003)</td>
</tr>
<tr>
<td>Epoietin alpha</td>
<td>Anemia due to chronic renal failure, HIV infected patients, chemotherapy, primary bone marrow disorders</td>
<td>50–150 IU/kg three times weekly</td>
<td>i.v</td>
<td>8 h</td>
<td>Hypertension, thrombotic complication, allergic reactions</td>
<td>Provenzano et al. (2005)</td>
</tr>
<tr>
<td>Darbepoietin alpha</td>
<td>Same as epoietin alpha</td>
<td>0.45 μg/kg once weekly</td>
<td>i.v/s.c</td>
<td>25 h</td>
<td>Mild transient injection site pain, rest same as epoietin alpha</td>
<td>Ibboston and Goa (2001)</td>
</tr>
<tr>
<td>Filgrastim (GM-CSF)</td>
<td>Cancer patients receiving myelosuppressive chemotherapy, patients with AML receiving either induction or consolidation chemotherapy, patients receiving BM transplant, peripheral blood stem cell transplantation (PBSC), severe chronic neutropenia</td>
<td>5 μg/kg/day for 14–21 days</td>
<td>i/v/s.c</td>
<td>3–5 h</td>
<td>Skeletal muscle pain, bone pain, alopecia, fever, rash, injection site reaction</td>
<td>Ibboston and Goa (2001), Neri et al. (2006)</td>
</tr>
<tr>
<td>Pegfilgrastim (pegylated GM-CSF)</td>
<td>Same as filgrastim</td>
<td>5–10 μg/kg/day for 4 days</td>
<td>s.c</td>
<td>45–60 h</td>
<td>Bone pain, myalgia, alopecia, fever, rash, edema</td>
<td>Schmidinger et al. (2004)</td>
</tr>
<tr>
<td>Sargramostim (G-CSF)</td>
<td>Following induction chemotherapy in patients with AML, to accelerate recovery after BM transplantation, PBSC</td>
<td>250 μg/m²/day for 7–10 days</td>
<td>s.c</td>
<td>2–5 h</td>
<td>Bone pain, malaise, fever, diarrhoea, edema, rash</td>
<td>Andre et al. (2003)</td>
</tr>
</tbody>
</table>
The mechanism of action of IFN-α-n3 has been evaluated in several multicentric trials. Intralesional injections of IFN-α-n3 (twice weekly) for up to eight weeks completely eliminated warts in 62% patients compared with only 21% of placebo-treated patients (Friedman-Kien et al., 1988). In another study, the efficacy of IFN-α-n3 has been studied in patients with warts refractory to previous treatment, overall, 80% of patients treated with IFN-α-n3 had a complete or partial resolution of genital warts compared to only 44% of those treated with placebo (Friedman-Kien, 1995). Side effects, usually flu-like symptoms, occurred briefly after the injections but disappeared before the end of the third week of therapy.

An emerging body of research suggests that IFN-alpha-n3 has anti-HIV activity and it is postulated that a combination of IFN-alpha-n3 with reverse transcriptase inhibitors and protease inhibitors may be of clinical utility in patients infected with HIV (ClinicalTrials.gov Identifier: NCT00215852).

### 4.3. Adverse effects of interferon-alpha

Injection site reactions are among the most common adverse reactions reported in clinical trials. Other common complaints are fever, fatigue, myalgia and headache. In addition, patients should be monitored closely with periodic clinical and laboratory evaluations, since treatment with alpha interferons may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. There have been some reports of depression and suicidal behavior with the use of interferon-alpha and because of this they require cautious use in patients with history of depression (Table 2). Patients with persistently severe or worsening signs or symptoms of these conditions should be withdrawn from therapy. In many but not all cases these disorders resolve after stopping interferon-alpha therapy.

### 4.4. Interferon-beta

**4.4.1. Interferon-beta-1a and interferon-beta-1b**

IFN-β-1a and 1b are glycoproteins containing 166 amino acids, produced by recombinant DNA technology. Interferon-β was the first clinically available agent demonstrated to be effective in modifying the disease course in patients with multiple sclerosis (Jonasch and Haluska, 2001). The efficacy of IFN-β-1a and β-1b in multiple sclerosis (MS) has been examined in large placebo-controlled, double-blind and numerous smaller studies. These studies demonstrated that IFN-β decreased relapses and probability of sustained clinical disability progression in patients with relapsing remitting MS (Weinstock-Guttman and Jacobs, 2000). Both forms of IFN-β had beneficial effects on disease process. IFN-β-1a had an additional benefit of slowing or preventing the development of MS-related brain atrophy (Weinstock-Guttman and Jacobs, 2000).

The mechanism of action of IFN-β in MS is not fully understood (Vilcek and Feldmann, 2004). IFN-β might act as an antagonist of endogenous IL-4 and particularly IFN-γ which is known to exacerbate MS. IFN-β also influences the function of blood brain barrier by inhibiting cell adhesion, cell migration and metalloproteinase activity thereby halting inflammation in the central nervous system. It also induces shift of cytokine profile to an anti-inflammatory phenotype (Vilcek and Feldmann, 2004).

IFN-β is now under clinical trials for the treatment of patients with intermediate uveitis. The purpose of this study (phase 3) is to investigate whether interferon-beta results in superior efficacy when compared to standard treatment with methotrexate for the treatment of intermediate uveitis and macular edema (ClinicalTrials.gov Identifier: NCT00344253).

### 4.5. Interferon-gamma

IFN-gamma is the principal cytokine for activating phagocytes and this effect is unique to IFN-γ which is not seen with other interferon preparations. Clinical studies in patients using recombinant IFN-γ have revealed a broad range of biological activities including enhancement of oxidative metabolism of tissue macrophages, enhancement of antibody dependent cellular cytotoxicity (ADCC) and natural killer (NK) cell activity. It also induces the production of major histocompatibility complex-I (MHC-I) molecules, MHC-II molecules, and co-stimulatory molecules by antigen presenting cells in order to promote cell-mediated immunity. It activates and increases the anti-microbial and tumoricidal activity of monocytes, macrophages, neutrophils, and NK cells (Sen and Lengyel, 1992; Shalaby et al, 1985).

#### 4.5.1. Interferon-gamma-1b

It is a genetically engineered recombinant cytokine containing 140 amino acids. Phagocyte stimulating effects of IFN-γ have been the basis for its approval in two rare conditions — severe, malignant osteopetrosis and chronic granulomatous disease. Treatment with IFN-γ-1b for both conditions greatly improves the ability of the patients to fight infectious diseases.

Severe, malignant osteopetrosis is a congenital condition which is life-threatening. The bone formation occurs at a near-normal rate, but there is a defect in bone resorption—the osteoclasts do not work effectively. The result of this imbalance is increased bone mass and reduced bone marrow cavity which is unable to support adequate development of blood cells, and the resulting thrombocytopenia, anemia, and infectious complications commonly cause death within the first decade of life. In a study that examined six patients suffering from osteopetrosis, the use of IFN-γ was found to be effective and a 96% decrease in the frequency of infections was noted. IFN-γ was found to increase bone resorption and hematopoiesis, and improve leukocyte function (Key et al., 1995). But more clinical evidence is needed to substantiate this fact.

Chronic granulomatous disease is an inherited disorder of phagocytic cells, which results from an inability of phagocytes to produce bactericidal superoxide anions (O2−). This leads to recurrent life-threatening bacterial and fungal infections. In a randomized, double-blind, placebo-controlled study in patients with chronic granulomatous disease, 128 patients were randomized to either receive IFN-γ (n=63) or placebo (n=65). IFN-γ produced a 67% decrease in relative risk of serious infections and a twofold reduction in the number of primary serious infections (30 on placebo versus 14 on IFN-γ,
IL-2, also known as T-cell growth factor is a potent immunomodulator whose major function is activation of various cells of immune system including helper T-cells, cytotoxic T-cells, B-cells, NK cells and macrophages. It mediates its action by binding to its corresponding cell surface receptor. At low doses IL-2 preferentially stimulates natural killer cells, while at higher doses delivered intermittently, it stimulates CD4+ cells to reproduce (Kovacs et al., 1996).

Aldesleukin is the genetically engineered product which possesses the biological activity of human native IL-2. It is the first FDA approved drug treatment for metastatic renal cell cancer (RCC), for which there is no standard treatment (Schmidinger et al., 2004). Another condition where aldesleukin has been approved includes metastatic melanoma refractory to conventional chemotherapy for multidrug-resistant pulmonary tuberculosis (Condos et al., 1997; Koh et al., 2004). Similar results from another study in which IFN-γ-1b was administered by subcutaneous route have been encouraging (Kim et al., 2004). However, further studies are needed to determine the optimum dose, the administration route and the duration of therapy with adjuvant IFN-gamma in patients with refractory multidrug-resistant TB.

### 4.6. Interleukin-2 (IL-2, aldesleukin)

IL-2, also known as T-cell growth factor is a potent immunomodulator whose major function is activation of various cells of immune system including helper T-cells, cytotoxic T-cells, B-cells, NK cells and macrophages. IL-2-stimulated cells thrive better in the face of HIV infection and Tavel, 2002). An emerging body of research suggests that IL-2-stimulated cells thrive better in the face of HIV infection than other CD4+ cells.

Chief dose-limiting toxic effects of IL-2 therapy in this setting include constitutional symptoms (fever, malaise, and fatigue) and asymptomatic hyperbilirubinemia (Kovacs et al., 1996).

Large scale studies are in progress to see if IL-2, in addition to anti-HIV therapy, reduces disease progression and prolongs life (ClinicalTrials.gov Identifier: NCT00001131, NCT00110812).

### 5. Anti-cytokines as therapeutic agents

#### 5.1. Tumor necrosis factor alpha inhibitors

Tumor necrosis factor family is primarily involved in the regulation of cell proliferation and apoptosis, but TNF-α has additional pro-inflammatory properties. TNF family receptors have four extracellular domains; they include receptors for soluble TNF-α and TNF-β as well as membrane-bound CD40 (important for B-cell and macrophage activation) and Fas (which signals the cell to undergo apoptosis).

TNF-α is a multifunctional cytokine which participates in the pathogenesis of various diseases including autoimmune, inflammatory, neurodegenerative diseases, diabetes, septic shock and congestive heart failure (Bazzoni and Beutler, 1996; Bolger and Anker, 2000; Singh and Suruchi, 2004). It is the principal cytokine that mediates acute inflammation, activates platelets and also plays a role in the genesis of fever, anemia and cachexia (Bazzoni and Beutler, 1996; O’Dell, 1999). TNF-α also mediates many of the inflammatory processes in rheumatoid arthritis (RA) including immune cell activation, proliferation and apoptosis and regulation of leukocyte movement. Indeed, the laboratory observation coupled with the studies in animal models has indicated the central role of TNF-α in rheumatoid arthritis and has led to the emergence of TNF blocking strategies.

Currently available anti-TNF-α strategies involve either administration of anti-TNF-α antibody or soluble TNF receptor to mop up circulating TNF-α. These inhibitors act by binding to TNF before it binds to receptors on nearby cells and prevent initiation of apoptosis or the inflammatory response.
The remarkable anti-inflammatory activity of the first neutralizing monoclonal anti-TNF antibody, infliximab, in RA patients has been well demonstrated (O’Dell, 1999; Maini and Taylor, 2000) and has subsequently stimulated the development of improved anti-TNF agents such as fully humanized antibody (adalimumab) and engineered fusion proteins of TNF soluble receptors and Fc fragments (etanercept), with reduced immunogenicity and a prolonged half-life.

While infliximab and adalimumab are recombinant monoclonal antibodies which bind only TNF-α, etanercept is a soluble TNF receptor fusion protein that binds to both TNF-α as well as TNF-β (Jarvis and Faulds, 1999).

Comparative features of 3 approved TNF inhibitors are mentioned in Table 3.

### 5.1.1. Indications

All 3 anti-tumor necrosis factor agents are approved for the treatment of rheumatoid arthritis, ankylosing spondylitis and Crohn’s disease. Only etanercept has been approved additionally for juvenile chronic arthritis since TNF-β is elevated in inflamed tissues in this condition.

Currently, anti-TNF blocking agents are the most promising therapy available for patients of rheumatoid arthritis unresponsive to standard disease modifying anti-rheumatic drugs (DMARDs) (Sharma et al., 2004). In contrast to older DMARDs, these agents have rapid onset of action with fewer side effects and have pronounced disease reducing activity when administered as monotherapy or in combination with methotrexate.

Since there have been no head to head trials comparing different TNF inhibitors, it is difficult to say which agent is more effective than the other and the choice of drug therefore depends on the patient’s preference and the prescriber’s experience with the particular TNF inhibitor. Recently, a literature analysis by Hochberg et al., revealed that the addition of either adalimumab, etanercept, or infliximab in patients who had an incomplete response to methotrexate is associated with a comparable response as defined by the American College of Rheumatology (ACR) criteria for 20% improvement i.e. ACR20 or American College of Rheumatology (ACR) criteria for 50% improvement i.e. ACR50 responder index after 24–30 weeks (Hochberg et al., 2003). However, additional studies are needed to better define the differences and optimize the clinical utilization of these agents.

The most common side effect seen in clinical trials with anti-TNF agents has been injection site reactions which do not require discontinuation of drug and becomes less prominent with continued use. Although, TNF inhibition is realized as an effective modality for treating autoimmune diseases, it does not come without potential cost to the host and there remains a risk of an increased rate of infection and malignancy. Thus, the major contraindications to the use of anti-TNF agents include previously untreated tuberculosis, recurrent chest infections or bronchiectasis and multiple sclerosis or demyelinating illness.

The scope of therapy using TNF-α blockers is now evolving to target other diseases like diabetes, psoriasis, asthma, malignancy and stroke (Singh and Suruchi, 2004). Currently, a randomized, double-blind, placebo-controlled trial is recruiting patients to investigate whether etanercept results in improved inflammatory indices, glucose tolerance and endothelial function in patients with metabolic syndrome (ClinicalTrials.gov Identifier: NCT00413400). Results of these studies are awaited and will throw light on the clinical usefulness of these cytokine inhibitors.

### 5.2. Interleukin-1 receptor antagonist

Interleukin-1 (IL-1) family genes encode three different peptides, IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1ra)

### Table 3

Comparative pharmacological and therapeutic status of infliximab, etanercept and adalimumab

<table>
<thead>
<tr>
<th></th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Chimeric (25% mouse/75% human) IgG1 monoclonal antibody</td>
<td>Recombinant fusion protein made of two soluble p75 TNF receptor and constant Fc portion of human IgG1</td>
<td>Fully humanized anti-TNF monoclonal IgG1 antibody</td>
</tr>
<tr>
<td><strong>Binds to</strong></td>
<td>Binds only TNF-α</td>
<td>Binds 2 molecules of TNF-α as well as TNF-β</td>
<td>Binds only TNF-α</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>3–10 mg/kg weekly at weeks 0, 2, 6; then every 2 months</td>
<td>25 mg twice a week</td>
<td>40 mg once in 2 weeks</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Intravenously</td>
<td>Subcutaneously</td>
<td>Subcutaneously</td>
</tr>
<tr>
<td><strong>Self administer</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>9–12 days</td>
<td>4–5 days</td>
<td>10–20 days</td>
</tr>
<tr>
<td><strong>Approved indications</strong></td>
<td>Rheumatoid arthritis (in combination with other DMARDs like methotrexate), Crohn’s disease, ankylosing spondylitis</td>
<td>RA (alone or in combination with methotrexate), ankylosing spondylitis, juvenile rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, psoriatic arthritis, Crohn’s disease</td>
<td>Moderate to severe RA (alone or in combination with methotrexate), ankylosing spondylitis, juvenile rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, psoriatic arthritis, Crohn’s disease</td>
</tr>
<tr>
<td><strong>Autoantibodies</strong></td>
<td>Neutralizing antibodies (7–53% after 5 infusions of 1–10 mg/kg)</td>
<td>Non-neutralizing antibodies</td>
<td>Neutralizing antibodies in vitro (8%)</td>
</tr>
<tr>
<td><strong>Tachyphylaxis</strong></td>
<td>Absent</td>
<td>Less allergic as compared to infliximab, mild injection site reactions, serious infections, TB and sepsis</td>
<td>Seen</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
<td>Acute infusion reactions—fever, chills, pruritis, chest pain, dyspnoea, flushing, urticaria, hypersensitivity reactions, serious infections, TB and sepsis</td>
<td>Injection site reactions, upper respiratory infections (sinus infections), headache, rash, nausea, serious infections, TB and sepsis</td>
<td></td>
</tr>
</tbody>
</table>
respectively (Mao et al., 2000). Like TNF-α, IL-1 production is induced in response to inflammatory stimuli and mediates various physiologic responses including inflammation and immune reactions. In normal homeostasis, the actions of IL-1 are maintained in balance by IL-1ra and other natural IL-1 inhibitors. However, a variety of diseases including autoimmune diseases, infections, solid tumors, leukemia, Alzheimer’s disease, trauma, hemodialysis, ischemic myocardial infarction, asthma, and graft versus host disease, are associated with increased IL-1 production (Dinarello, 1996).

IL-1 is also strongly implicated in the pathogenesis of rheumatoid arthritis where it causes cartilage degradation by rapid loss of proteoglycans as well as stimulation of bone resorption. Thus, a biologically active engineered product of IL-1ra, anakinra, has been developed for clinical use in this condition.

5.2.1. Anakinra

It is the recombinant non-glycosylated form of human IL-1 ra (rhIL-1ra) produced in Escherichia coli and is approved for use in the treatment of patients with RA unresponsive to one or more disease modifying anti-rheumatic drugs (DMARDs). Anakinra blocks the biologic activity of IL-1 by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL-1RI), which is expressed in a wide variety of tissues and organs.

The safety and efficacy of anakinra has been evaluated in several randomized controlled trials in combination with other disease modifying anti-rheumatic drugs or as a monotherapy (Nuki et al., 2002; Fleischmann et al., 2003; Cohen et al., 2002; Kavanaugh, 2006). In all the studies, patients treated with anakinra in combination with methotrexate achieved an ACR20 or higher magnitude of response (ACR50 and ACR70) than patients treated with methotrexate and placebo.

The most commonly reported adverse event was injection site reaction. However, the major concern with anakinra use is the risk of serious infections and it is therefore contraindicated in the presence of active infection. Because of the same reason anakinra should not be used in conjunction with anti-TNF-alpha agents. In addition, patients should also be monitored for reversible thrombocytopenia and neutropenia, the latter exacerbated by concomitant methotrexate use.

In the present scenario, both IL-1 receptor antagonist and TNF-α blockers have proved to be as efficacious as conventional DMARDs, however their enormous cost and potential to cause long term side effects remain a concern. Therefore, randomized head-to-head studies are needed to determine which of these drugs are most effective and safe for rheumatoid arthritis.

Other disease states for which anakinra is under research and may prove to be of therapeutic benefit include cerebral ischemia, severe sepsis, acute stroke, diabetes, asthma and inflammatory bowel disease (Loddick and Rothwell, 1996; Opal et al., 1997; Emsley et al., 2005).

5.3. IL-2 receptor antagonists

Interleukin-2 receptor (IL-2R) is a heterotrimeric protein composed of α, β and γ chains (Minami et al., 1993). The α and β chains are involved in binding IL-2, while signal transduction following cytokine interaction is carried out by the γ-chain, along with the β subunit. IL-2R is expressed on the surface of certain immune cells, such as antigen-activated T-cells, B-cells and is involved in their proliferation. Thus, the number of disease states is linked to over-expression of IL-2R-α such as autoimmune diseases, allograft rejection, a variety of lymphoid neoplasms like adult T-cell leukemia (ATL), mycosis fungoides, peripheral T-cell lymphoma, hairy cell leukemia, Hodgkin's disease and some B-cell neoplasms (Morris and Waldmann, 2000).

Because there is a definite link between IL-2R-α over-expression and occurrence of several diseases, therapies have evolved to curb IL-2R-α over activity. One approach to inhibit IL-2-induced T-cell proliferation is through monoclonal antibody directed against the alpha chain of IL-2 receptor. Two such monoclonal antibody preparations available for use include basiliximab and daclizumab, a chimeric and a humanized antibody, respectively (Gelder et al., 2004) (Table 2). These are approved for prophylaxis of acute organ rejection in renal transplant patients in combination with other immunosuppressive agents (glucocorticoids, cyclosporine). Basiliximab induction demonstrated an excellent safety profile, with no increase in the incidence of malignancy, infections or death (Ramirez and Marino, 2007). Results of clinical trials have shown that both these drugs are equally efficacious and allow the use of corticosteroid free regimens in renal transplant recipients (Chapman and Keating, 2003). The overall efficacy, tolerability, ease of administration and cost effectiveness make these drugs an attractive option for prophylaxis.

Other approaches to IL-2R targeted treatment of various cancers are under study and include use of ligand–toxin fusion protein and immunotoxins (Saleh et al., 1998; Kreitman et al., 2000).

6. Chemokines

Chemokines are small peptides that are potent activators and chemoattractants for leukocyte subpopulations and some non-hematopoietic cells. These chemotactic cytokines belong to the chemokine superfamily, which can be divided into 4 groups or families (CXC, CX3C, CC, and C) based on a cysteine motif. Their actions are mediated by a family of 7-transmembrane G-protein-coupled receptors (Onuffer and Horuk, 2002). Chemokines are known to function as regulatory molecules in leukocyte maturation, traffic, homing of lymphocytes and in the development of lymphoid tissues. Besides these functions in the immune system, they also play a critical role in many pathophysiological processes such as allergic responses, infectious and autoimmune diseases, angiogenesis, inflammation, tumor growth and hematopoietic development (Onuffer and Horuk, 2002). Alteration and inappropriate expression of chemokine receptors is thought to be implicated in multiple sclerosis, asthma, some cancers, rheumatoid arthritis and some cardiovascular diseases.

In addition, certain chemokines and their receptors are involved in HIV pathogenesis. The discovery of chemokine receptors as co-receptors for HIV-1 has opened the door for a number of novel anti-viral approaches.
As knowledge of the role of chemokine receptors has expanded from autoimmunity to AIDS, the importance of these intervention therapies has grown. The promise of highly specific therapies for several diseases, based on chemokine receptor antagonists, is on the horizon.

In the present review our focus was mainly on approved cytokines and anti-cytokine agents (Table 2); however, many other agents are emerging for use in a wide range of medical settings (Table 4).

### 7. Other cytokines of possible importance

Numerous other cytokines, including IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-18, IL-21, etc. have been used experimentally in animals and are being tried in patients for various conditions, but have not yet reached the market. The list of few such cytokines is mentioned in Table 4.

### 8. Future perspectives

Cytokine therapy has and will be successful when disease-causing mechanisms are relatively "simple" and cytokine driven. However, given the pleiotropic and redundant nature of cytokines, a future direction in complex disorders may be the simultaneous inactivation/activation of multiple cytokines.

The latest development in the field of cytokines is the use of cytokine gene therapy for treatment of various cancers (Podhajcer et al., 2007). But the real effectiveness of this approach would be evident only with further studies in times to come.

### 9. Conclusion

Increasingly, cytokine-based drugs and anti-cytokines are playing a crucial role in the understanding of pathogenesis as well as management of several diseases. Research is continuing with an aim to develop new therapies, refine those already in use, and establish the safest and most effective dosage levels. Due to these on-going studies, it is imperative for clinicians to stay abreast with the latest information for the benefit of their patients.

### References


Skurkovich, S.V., Skurkovich, B., 1989. Development of autoimmune diseases is connected with the initial disturbance of IFN synthesis in the cells. J. IFN Res. 9 (Suppl. 2), S305.


