Ocular Immunotherapy and Immunomodulation

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Immunotherapy is a hot topic in ophthalmology because of the recent advancements in cellular and intracytoplasmic mechanisms that control inflammation and immunology. There are many suspected ocular surface and intraocular inflammatory diseases that are thought to be mainly immune-mediated in origin or involved in the disease pathogenesis. Steroidal medications are the most frequently used “immunotherapy” medication in veterinary medicine. However, this drug is truly taking the “sledge hammer” approach to therapy, with lots of peripheral damage (i.e., side effects). Steroidal and non-steroidal therapy will be reviewed in other lectures. The newer medications are designed to be more specific in their treatment approach and thus, have fewer side effects. Most of these medications are systemically administered, although local injections, including intraocular injections, are being evaluated in humans and experimentally. Please see the accompanying recent review article that extensively reviews immunomodulating medications in human ocular disease (Surv Ophthalmol 56:474-510, 2011). Also see the Vet Clinics of North America publication on use of immuosuppressive drugs in dogs and cats (Vet Clin Small Anim 43 (2013) 1149–1170). The ocular penetration, both topically and via the systemic route have not been studied extensively for many drugs, but one would assume that with the blood-aqueous barrier disrupted, most blood-borne medications should enter the eye easily. The purpose of these notes and lectures is to review existing and emerging immunomodulation drugs to better our understanding of immunotherapy of ocular disease.

Corticosteroids are used as first-line treatment for many ocular inflammatory conditions. The risk of adverse effects, however, necessitates conversion to steroid-sparing immunomodulatory therapy (IMT) for disease that is recurrent, chronic, or poorly responsive to treatment. Immunomodulatory agents include the broad categories of antimetabolites (azathioprine, methotrexate, mycophenolate mofetil), alkylating agents (cyclophosphamide, chlorambucil), T-cell inhibitors (cyclosporine, tacrolimus, sirolimus), cytokine or cytokine receptor inhibitors (Etanercept, infliximab, adalimumab, and anakinra), immunosuppressive cytokines (IL-10, TGFβ), and oral tolerance.

Conventional Immunomodulatory Agents in Ocular Inflammatory Disease

Antimetabolites

AZATHIOPRINE (Azasan®; Imuran®)

*Description:* Azathioprine is an immunosuppressive antimetabolite pro-drug, converted in the body to the active metabolite 6-mercaptopurine.
**Mode of action:** Azathioprine acts to inhibit purine synthesis necessary for the proliferation of cells, especially leukocytes and lymphocytes. Its most severe side effect is bone marrow suppression.

**Use in Veterinary Medicine:** Azathioprine is used mainly in dogs for treatment of nodular granulomatous episclerokeratitis (NGE) and non-infectious uveitis, chorioretinitis, and optic neuritis.\(^1,2\) This drug is usually used in combination with systemic corticosteroids and used frequently to lessen the side effects of long-term steroid use or when steroids alone are not effective. Has been largely replaced in human medicine by the use of cyclosporine and Mycophenolate mofetil (see more information below).\(^3\)

**METHOTREXATE (Rheumatrex®)**

**Description:** Methotrexate is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, adult rheumatoid arthritis, and some non-infectious uveitis in humans.\(^3-5\)

**Mode of action:** Methotrexate acts by inhibiting the metabolism of folic acid. Methotrexate competitively and reversibly inhibits dihydrofolate reductase, an enzyme that is part of the folate synthesis metabolic pathway. Dihydrofolate reductase catalyses the conversion of dihydrofolate to the active tetrahydrofolate. Folic acid is needed for the de novo synthesis of the nucleoside thymidine, required for DNA synthesis. Methotrexate, therefore, inhibits the synthesis of DNA, RNA, thymidylates, and proteins.

**Use in Veterinary Medicine:** There are no descriptions of the use of methotrexate in uveitis in veterinary medicine, but has been used as a chemotherapeutic agent in dogs.\(^6\)

**MYCOPHENOLATE MOFETIL (CellCept®)**

**Description:** Mycophenolate mofetil (MMF) is the mofetil ester of mycophenolic acid the active immunosuppressant. MMF has largely replaced azathioprine in human medicine in organ transplants, is used for myasthenia gravis, and is increasingly used for human uveitis.\(^3,7,8\) Topical MMF has been shown to penetrate the cornea.\(^9\)

**Mode of action:** MMF inhibits T and B cell proliferation by blocking the production of guanosine nucleotides required for DNA synthesis. MMF inhibits the proliferation of lymphocytes, fibroblasts, endothelial cells, and arterial smooth muscle cells. MMF is a selective inhibitor of inosine monophosphate dehydrogenase, thus blocking purine synthesis via the de novo pathway preferentially used by T and B lymphocytes.

**Use in Veterinary Medicine:** We currently have a clinical trial ongoing here at NCSU (monitored by Drs. Freya Mowat and Whitney Young) evaluating MMF for treatment SARDS. There is a report of using MMF in uveodermatologic syndrome in dogs (Kang et al. Can Vet J. 2014 Jun; 55(6): 585–588).

**Alkylating Agents**

**CYCLOPHOSPHAMIDE (Cytoxan®)**
**Description:** Cyclophosphamide is a nitrogen mustard alkylating agent, used to treat various types of cancer and some autoimmune disorders in humans. Cyclophosphamide is used in combination with other medications in the treatment of uveitis.  

**Mode of action:** Cyclophosphamide is converted by mixed function oxidase enzymes in the liver to active metabolites. The main active metabolite is 4-hydroxycyclophosphamide. This phosphoramidate mustard forms DNA crosslinks between and within DNA strands, which leads to cell death. 

**Use in Veterinary Medicine:** Cyclophosphamide has been used in dogs as a steroid sparing medication in uveitis and in ocular lymphoma.  

**CHLORAMBUCIL** (Leukeran®)  

**Description:** Chlorambucil is a nitrogen mustard alkylating agent. Chlorambucil is used primarily in humans as an antineoplastic agent to treat chronic lymphocytic leukemia, and primary macroglobulinemia. It also is an immunosuppressive agent that has been used to treat systemic lupus erythematosus, acute and chronic glomerular nephritis, nephrotic syndrome, psoriasis, Wegener’s granulomatosis, and chronic active hepatitis. 

**Mode of action:** Alkylating agents interfere DNA replication, and prevent cellular division of rapidly proliferating cells, such as inflammatory and neoplastic cells. 

**Use in Veterinary Medicine:** In dogs, it is used primarily as a chemotherapeutic agent but has been used in dogs as a steroid sparing medication in uveitis. 

**T-cell Inhibitors** 

**CYCLOSPORINE** (Neoral®, Atopia®, Optimmune®, Restasis®)  

**Description:** Cyclosporine (CsA) is a powerful immunosuppressive drug and part of a growing family of calcineurin inhibitors. CsA was isolated from the fungus, *Tolypocladium inflatum* in 1976. It is a lipophilic, neutral cyclic undecapeptide and is the first immunosuppressant to have a selective effect on lymphoid or T-cells. This effect on T-cells is unique: at therapeutic concentrations it inhibits T-cell proliferation but is non-cytotoxic. CsA was initially used to prevent allograft rejection and graft–virus–host disease. It is now used for a variety of ocular and non-ocular conditions. 

**Mode of action:** CsA exerts a major therapeutic effect by inhibiting T-lymphocyte activation. This occurs early in the T-cell activation cycle and likely leads to failure of activation of
early gene transcription, such as those encoding cytokines, e.g., IL2, IL4 and gamma interferon. The lack of activation of these genes prevents the proliferation of lymphocytes.

CsA interferes with the expression of IL2 receptors on the surface of T-lymphocytes and also with IL2 release from lymphocytes. CsA blocks transcription of mRNA specific for production of IL2, IL4, and gamma interferon. The proteins bonding to the IL2 enhancer for transcription regulation appear to be at the point CsA inhibits transcription. CsA is bound in cytoplasm by cyclophylline or immunophylline, which is an abundant and ubiquitous protein (17 kilodaltons) found in both procaryotic and eucaryotic organisms. The CsA–immunophylline combination is bound in cytoplasm to a calcium-dependent protein phosphorase called calcineurin. Antigen production at the CD3 receptor causes an increase in intracellular calcium concentration and activation of the phosphatase activity of calcineurin. Calcineurin binds with high affinity to biologically active immunophylline or to immunophylline drug complexes. The CsA–calcineurin–immunophylline complex will block the ability of calcineurin to translocate transcription factors, such as NF-AT, into the nucleus, thus preventing transcription and gene expression (see Figure).

**Mechanism of action of cyclosporin.** The cyclosporine-calcineurin-cyclophilin (immunophylline) complex blocks the ability of calcineurin to dephosphorylate and translocate nuclear factor AT (NF-AT) into the nucleus. This blocks the activation of transcription of proinflammatory cytokines which help to initiate early immune response; Ca\(^{2+}\)=increased cytoplasmic calcium levels from activation of CD3/CD4 complex by antigen.

**Use in Veterinary Medicine:** In veterinary ophthalmology, CsA is most commonly used for treatment of immune-mediated canine keratoconjunctivitis sicca (KCS). Topical CsA has also been shown to be effective in treating chronic superficial keratitis, or pannus, in dogs. We have also used topical CsA for management of a variety
of presumed immune-mediated ocular diseases such as canine nodular granulomatous episclerokeratitis, equine immune-mediated keratitis,\textsuperscript{16} and for the prevention of rejection of corneal grafts.

Oral CsA is effective in immune-mediated uveitis in the horse and dogs. In dogs, oral CsA is effective, but expensive. In horses, several types of ocular implants have been shown to effectively prevent ERU episodes.\textsuperscript{13,14,19,25,26}

In addition, CsA has been demonstrated to inhibit growth of leptospiral organisms\textsuperscript{19} and other micro-organisms including viruses such as hepatitis C,\textsuperscript{27} and herpesvirus;\textsuperscript{28} protozoa such as \textit{Leishmania}\textsuperscript{29} and \textit{Toxoplasma}.\textsuperscript{30}

\textbf{TACROLIMUS (FK-506; Fujimycin; Prograf\textsuperscript{®})}

\textit{Description:} Tacrolimus is a macrolide lactone discovered in 1984 from the fermentation broth of a Japanese soil sample that contained the bacteria \textit{Streptomyces tsukubaensis}. It has similar immunosuppressive properties to cyclosporine, is also considered a calcineurin inhibitor, but is much more potent in equal volumes than cyclosporine (20 to 50 times more potent). Most studies of ocular inflammation demonstrate equal efficacy to CsA but a better safety profile with Tacrolimus.\textsuperscript{3,18}

\textit{Mode of action:} Tacrolimus binds to the immunophilin FKBP-12 (FK506 binding protein) that inhibits calcineurin thus inhibiting both T-lymphocyte signal transduction and IL-2 transcription, similar to cyclosporine.

\textit{Use in Veterinary Medicine:} Systemic tacrolimus is more toxic in dogs than CsA, so systemic use has been limited.\textsuperscript{31} Topical 0.02\% tacrolimus has shown efficacy in canine KCS,\textsuperscript{32} but safety studies have not been published. Owners should be warned of the recent FDA black-box warning of cancer risk with use of topical tacrolimus (http://www.fda.gov/cder/drug/infopage/protopic/default.htm).

\textbf{SIROLIMUS (Rapamycin, Rapamune\textsuperscript{®})}

\textit{Description:} Sirolimus is a macrolide antibiotic discovered as a product of the bacterium \textit{Streptomyces hygroscopicus} in a soil sample from Easter Island. It was originally developed as an antifungal agent until the potent immunomodulating activity was discovered. RAPA has been shown to prevent corneal allograft rejection, reduce ocular inflammation in uveitis, and has been shown to be non-toxic when injected intravitreally in rabbits.\textsuperscript{33-35} Recently, we found that RAPA was not toxic when injected intravitreally in horses. RAPA has been
suggested to be photosensitive, but we did not see evidence of this in our *in vitro* studies.\(^{36}\)

**Mode of action:** Sirolimus is not a calcineurin inhibitor but has similar suppressive effect by blocking activation of T- and B-cells. RAPA binds to the immunophilin FK506 binding protein to create an immunosuppressive complex that inhibits the mammalian target of rapamycin (mTOR). The inhibition of mTOR prevents the cell cycle from progressing from G1 to the S phase, leading to the suppression of T-lymphocyte activation and proliferation.

**Use in Veterinary Medicine:** This drug has much promise since it does not exhibit renal toxicity in people and has been shown to be effective in treatment of uveitis.\(^{33}\) Clinical trials are underway to determine effectiveness of intravitreal RAPA in ERU horses.

### Novel Immunomodulatory Agents

#### Antibodies

**Cytokine or Cytokine-Receptor Inhibitors**

**ETANERCEPT (Enbrel®)**

**Description:** Etanercept a human recombinant, soluble tumor necrosis factor-alpha (TNF\(\alpha\)) receptor. It is a small protein (p75, i.e., its molecular weight is 75 kDa) that binds TNF\(\alpha\) and decreases its role in inflammatory diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, and ankylosing spondylitis. There are reports of use of
etanercept in human uveitis, optic neuritis, and has been demonstrated to be safe experimentally injected intravitreally.\textsuperscript{34-37}

**Mode of action:** Two distinct TNF receptors, a 55-kilodalton and a 75-kilodalton protein, exist naturally as monomeric molecules on cell surfaces. The biological activity of TNF is dependent on binding to either cell-surface receptor. Etanercept is a dimeric, soluble form of the 75-kilodalton TNF receptor. The anti-inflammatory effects of etanercept are due to its ability to bind to TNF, preventing it from interacting with cell-surface receptors and rendering it biologically inactive. Etanercept can also modulate biological responses that are induced or regulated by TNF, including both expression of adhesion molecules responsible for leukocyte migration and serum levels of cytokines and matrix metalloproteinase-3.

**Use in Veterinary Medicine:** There are no descriptions of the use of etanercept in uveitis in veterinary medicine.

INFLIXIMAB (Remicade\textsuperscript{®})

**Description:** Infliximab is a chimeric monoclonal antibody. Infliximab binds specifically to human tumor necrosis factor alpha (TNFa). Infliximab is used to treat human rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, psoriatic arthritis, and ankylosing spondylitis. Its side effects of increased infection, especially tuberculosis, has limited it use recently in people. It has been used for treatment of human uveitis and posterior uveitis.\textsuperscript{34,36,38}

**Mode of action:** Infliximab, a chimeric (mouse Fv1, human IgG1) monoclonal antibody, specifically binds to both soluble and membrane-bound TNFα with high affinity forming stable nondisassociating immune complexes. The binding of infliximab to TNFα prevents the binding of TNFα to its receptors and blocks the initiation of the intracellular signaling that leads to gene transcription and subsequent biologic activity, similar to enteracept. The main difference is that enteracept is administered weekly SQ, while infliximab is given IV every 2 months.

**Use in Veterinary Medicine:** There are no descriptions of the use of infliximab in uveitis in veterinary medicine.

ADALIMUMAB (Humira\textsuperscript{®}) and EFALIZUMAB (Raptiva\textsuperscript{®})

**Description:** Both Adalimumab and Efalizumab are TNFalpha inhibitors. Adalimumab is for treatment of rheumatoid arthritis and Efalizumab is for treatment of severe psoriasis. There is one report on the effective use of adalimumab for treatment of human uveits.\textsuperscript{39}

**Mode of action:** Same as for enteracept and infliximab

**Use in Veterinary Medicine:** There are no descriptions of the use of these medications for uveitis in veterinary medicine.
ANAKINRA (Kineret®)

**Description:** Anakinra is a recombinant, nonglycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra). It is approved for treatment of rheumatoid arthritis in humans, especially for those who do not respond to anti-TNF therapy. Experimentally, IL-1 antagonists decrease uveitis in mice and topically help prevent corneal graft rejection in rats.

**Mode of action:** IL-1 binds to the IL-1 receptor type 1 (IL-1RI), which triggers the inflammatory response. Immune-mediated inflammation, such as that in rheumatoid arthritis, triggers an increase in the production of cytokines, including IL-1, in the affected areas. In some cases, the increase in IL-1 production is such that it overwhelms the development of IL-1Ra. Excessive levels of IL-1 have been associated with tissue damage. The goal of the IL-1 receptor antagonist (IL-1Ra) is to help provide a balance against the destructive effects of an overabundance of IL-1.

**Use in Veterinary Medicine:** There are no descriptions of the use of these medications for uveitis in veterinary medicine.

DACLIZUMAB (Zenapax®)

**Description:** Daclizumab is a murine-human chimaerised monoclonal antibody to the IL-2Rα receptor of T cells. It is used to prevent rejection in organ transplantation, especially in kidney transplants. In a clinical trial in humans, daclizumab (2mg/kg q2 weeks, then 1 mg q2 weeks) was shown to lower corticosteroid requirement in humans with non-infectious uveitis, without side-effects.

**Mode of action:** Daclizumab binds specifically to the alpha subunit (p55 alpha, CD25, or Tac subunit) of the human high-affinity interleukin-2 (IL-2) receptor that is expressed on the surface of activated lymphocytes.

**Use in Veterinary Medicine:** There are no descriptions of the use of these medications for uveitis in veterinary medicine.

TOCILIZUMAB

**Description:** Tocilizumab a recombinant humanized anti-IL-6 receptor monoclonal antibody that has been shown to bind specifically to both soluble and membrane-bound IL-6 receptor and inhibit downstream signaling by these receptors. It is used in the treatment of moderate to severe rheumatoid arthritis. There are no reports of its use in clinical patients.

**Mode of action:** Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptor.

**Use in Veterinary Medicine:** There are no descriptions of the use of these medications for uveitis in veterinary medicine.

Immunosuppressive Cytokines

INTERLEUKIN-10
**Description:** Interleukin-10 (IL-10) is a multifunctional cytokine with diverse effects on most hemopoietic cell types and acts to limit and ultimately terminate inflammatory responses. In addition to these activities, IL-10 regulates growth and/or differentiation of B cells, NK cells, cytotoxic and helper T cells, mast cells, granulocytes, dendritic cells, keratinocytes, and endothelial cells. Viral IL-10 adenovirus (Ad-vIL-10)-mediated gene transfer has experimentally reduced uveitis in animal models.\(^{43-45}\)

**Mode of action:** IL-10 inhibits activation and effector function of T cells, monocytes, and macrophages. It accomplishes this by two major methods: (1) inhibit cytokine (i.e., TNF, IL-1, chemokine, and IL-12) production by macrophages and (2) to inhibit the accessory functions of macrophages in T cell activation by reduced expression of MHC class II molecules and certain co-stimulators (e.g., B7). The cumulative effect of these functions acts to inhibit T cell-mediated immune inflammation.

**Use in Veterinary Medicine:** There are no descriptions of the use of these medications for uveitis in veterinary medicine.

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**TRANSFORMING GROWTH FACTOR BETA**

**Description:** Transforming growth factor-beta is widely distributed throughout the body and plays an important role in the ocular immune response and is predominantly immunosuppressive. Three isoforms (β1, β2, β3) of TGF-β have been identified in mammals and they share 70-99% sequence homology across species. Three major signal-transducing receptor types for TGF-β have also been identified. Number, maintenance and proportion of TGF-β receptors have a pivotal role in the biologic effects exerted by the TGF-β protein. The biological interactions of TGF-β are complex, and direct therapy and anti-TGF-B therapies for specific ocular diseases are being evaluated experimentally.

**Mode of action:** Transient upregulation of TGF-β expression is important for normal wound repair, whereas sustained overproduction of this growth factor contributes to tissue fibrosis. In lower concentrations TGF-β has some pro-inflammatory properties, while at higher concentrations its effects are primarily immunosuppressive. TGF-β operates by both autocrine and paracrine modes to control proliferation of cells of the immune response, generally suppressing responses of Th1 cells, but stimulating the fibrotic component of the chronic inflammatory response.

**Use in Veterinary Medicine:** There are no descriptions of the use of these medications for ocular disease in veterinary medicine.

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**HUMAN INTRAVENOUS IMMUNOGLOBULIN**

**Description:** hIVIg is a purified product of pooled human plasma from multiple healthy donors and due to the large number of donors, these preparations provide a broad spectrum of antibody specificities against pathogens. Approximately 90% of hIVIg is purified IgG with trace concentrations of IgA, IgM, CD4, CD8, and HLA molecules. In the treatment of immune-mediated diseases, hIVIg is used for its ability to regulate the immune system, inhibit phagocytosis, and decrease tissue damage. It has been used in a variety of human ocular diseases, such as uveitis, optic neuritis, graves ophthalmopathy, VKH, and Becets disease, with varying levels of success.

**Mode of action:** The immunomodulatory actions of hIVIg are not well understood but the efficacy of hIVIg therapy in the treatment of immune-mediated diseases has been attributed to multiple mechanisms: (1) blockage and modulation of the IgG Fc fragment receptors on
the surface of macrophages; (2) modulation of cytokine synthesis and release; (3) modulation of the complement system; (4) selection of B- and T-lymphocyte repertoires; (5) neutralization of circulating autoantibodies; and finally (6) interaction with other B- and T-lymphocyte surface molecules. Adverse effects include aseptic meningitis, allergic reactions, and transmission of blood-borne infections. No significant adverse effects have been reported in association with hIVIG administration in clinically ill dogs and cats.

**Use in Veterinary Medicine:** The high cost has limited the use in veterinary medicine. There are anecdotal descriptions of use of IVIg therapy in SARDs cases.

**Oral Tolerance**

*Description:* Oral tolerance is an induction of peripheral immune non-responsiveness as the result of the oral administration of soluble protein antigens. It is considered a natural, continuous immunologic mechanism, driven by exogenous antigens, to avoid untoward immune responses in the gut. In a pilot study in humans with immune-mediated uveitis fed S-antigen led to immunosuppressive medications being decreased and/or stopped. Oral tolerance is an inducement of immune non-responsiveness as the result of the oral administration of soluble protein antigens. It is considered a natural, continuous immunologic mechanism, driven by exogenous antigens, to avoid untoward immune responses in the gut. In a pilot study in humans with immune-mediated uveitis fed S-antigen led to immunosuppressive medications being decreased and/or stopped.

*Mode of action:* The initial antigen/gut associated lymphoid tissue (GALT) interaction is crucial to develop oral tolerance. With low doses of antigen, orally tolerance appears to take place at the level of the gut, with Th2 cells generated. Possibly specific IL-4/IL-10 and/or TGF-beta producing cells are induced. These cells migrate to immune organs, where they will down-regulate antigen-specific responses. High doses of antigen may result in clonal depletion of immune cell populations.

*Use in Veterinary Medicine:* There are no descriptions of the use of these medications for ocular disease in veterinary medicine.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Mol Wt</th>
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<td><strong>Antimetabolites</strong></td>
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<td>Azathioprine</td>
<td>Azasan®, Imuran®</td>
<td>277.264</td>
<td>NGE, uveitis, chorioretinitis</td>
<td>Dog: 2 mg/kg PO qd x 2 wks; then 1 mg/kg qod, then 1 mg/kg once weekly for 30d.⁴⁹</td>
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<td>Methotrexate</td>
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<td><strong>Alkylating Agents</strong></td>
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<td>Uveitis</td>
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<td><strong>T-cell Inhibitors</strong></td>
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**Immunosuppressive Cytokines**

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**Oral Tolerance**

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<td>NYR</td>
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*Please check accuracy of all doses prior to therapy.

NYR – Not yet reported.

**REFERENCES**