

BRIEF ARTICLES

Ixekizumab Overdose: A Case ReportMargaret L. Snyder, MD¹, Mark G. Lebwohl, MD¹¹Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY**ABSTRACT**

Biologics, defined as medicinal products derived from living cells, are currently some of the most studied pharmaceutical agents and constitute a large portion of recent therapeutic breakthroughs in clinical trials. Relatively novel to the scientific and medical community, insulin was the first biologic agent to be FDA-approved in the 1980's.¹ Since that time, the development of therapeutic monoclonal antibodies by Milstein and Kohler has revolutionized modern medicine, with over 100 products currently on the market for the prevention and treatment of infectious, neoplastic, autoimmune, and inflammatory diseases.^{2,3} Despite the remarkable clinical success that monoclonal antibodies have achieved since their development, safety data is still limited due to the relatively short duration of time these products have been available. Specifically, there is a considerable paucity of information regarding inadvertent biologic overdose, with most package inserts simply advising clinicians to monitor their patients for symptoms. Due to complex dosing schedules as well as increasing use of these agents, it is likely that healthcare providers will encounter cases of patients accidentally self-administering larger than recommended doses. It is thus imperative to have more data on maximum tolerated doses in order for clinicians to educate and care for their patients in the case of accidental biologic overdose. We therefore present a case of inadvertent administration of a higher than recommended dose of ixekizumab and review the available literature on biologic overdoses.

INTRODUCTION

Biologics, defined as medicinal products derived from living cells, are currently some of the most studied pharmaceutical agents and constitute a large portion of recent therapeutic breakthroughs in clinical trials. Relatively novel to the scientific and medical community, insulin was the first biologic agent to be FDA-approved in the 1980's.¹ Since that time, the development of therapeutic monoclonal antibodies by Milstein and Kohler has revolutionized modern medicine, with over 100 products currently on the market for the prevention and treatment of infectious, neoplastic, autoimmune, and inflammatory diseases.^{2,3}

Despite the remarkable clinical success that monoclonal antibodies have achieved since their development, safety data is still limited due to the relatively short duration of time these products have been available. Specifically, there is a considerable paucity of information regarding inadvertent biologic overdose, with most package inserts simply advising clinicians to monitor their patients for symptoms. Due to complex dosing schedules as well as increasing use of these agents, it is likely that healthcare providers will encounter cases of patients accidentally self-administering larger than recommended doses. It is thus imperative to have more data on maximum tolerated doses in order for clinicians to educate and care for their patients in the case of accidental biologic

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overdose. We therefore present a case of inadvertent administration of a higher than recommended dose of ixekizumab and review the available literature on biologic overdoses.

CASE PRESENTATION

A 69-year-old male with chronic plaque psoriasis presented to clinic for follow up after previously failing multiple therapies, including: etanercept, adalimumab, infliximab, ustekinumab, and risankizumab. The patient was initiated on ixekizumab 160 mg subcutaneously (two syringes, loading dose) at week 0, followed by instructions to administer 80 mg subcutaneously (one syringe, maintenance dose) on weeks 2, 4, 6, 8, 10, and 12. During week 7 of therapy, the pharmacy called and informed us that the patient had injected two syringes (total of 160 mg) on weeks 2, 4 and 6. Upon further questioning, it became apparent that the patient misunderstood the instructions and had inadvertently administered twice the recommended dose on these weeks. He did not experience any adverse effects, but did notice significant improvement in his psoriatic lesions. The patient was instructed to hold the medication for one month, after which time he initiated the recommended dose of one syringe (80 mg) on weeks 10 and 12. He is now on the recommended medication regimen and continues to do well with no adverse effects.

DISCUSSION

Despite biologic agents being one of the fastest growing domains of pharmaceutical research with increasing numbers of new drugs approved for market use every year, there is very little data regarding inadvertent drug overdose. In fact, most information available to clinicians is limited to package

inserts or online prescribing information pages, and even these often exclusively include a generic statement such as “In the case of inadvertent overdose, monitor the patient for signs and symptoms of adverse effects”. This paucity of guidance for clinicians limits their ability to adequately counsel and monitor their patients in the event a higher than recommended dose of biologic medication is accidentally administered, either by the patient themselves or by healthcare personnel. We therefore report a case of inadvertent overdose of ixekizumab in order to augment the scientific literature and equip healthcare providers and patients with more pertinent information.

By nature of their chemical structure as “large molecules”, biologic agents must be injected intravenously or subcutaneously. Due to the pharmacokinetic properties and bioavailability of these agents, it is common for a larger “loading dose” injection to be used to initiate treatment, followed by a lower “maintenance dose” to be administered at specific time intervals, depending on the medication and its indication for use. Due to this inconsistency with dosing, it is easy to imagine how patients may become confused while self-administering at home, even in the most controlled of circumstances, such as during a clinical trial. For example, in the ASCERTAIN trial comparing the safety and efficacy of sarilumab and tocilizumab in rheumatoid arthritis, accidental overdose of tocilizumab occurred in 8.8% of patients.⁴ Thankfully, dose-limiting toxicities are often not observed; in fact, a single IV overdose of up to 40 mg/kg of tocilizumab has been reported with no adverse drug reaction.⁵ Furthermore, package inserts/prescribing information pages report administration of higher than currently recommended doses

Table 1.

Citation	Drug Overdose	Biologic Target	Effect
Tocilizumab Package Insert	Tocilizumab, one case of 40 mg/kg single IV infusion	IL-6	No adverse drug reactions observed
Tocilizumab Package Insert	Tocilizumab, 5 healthy volunteers received 28 mg/kg single dose	IL-6	All 5 patients developed dose-limiting neutropenia; there were no serious adverse reactions
Infliximab Package Insert	Infliximab, 20 mg/kg single dose	TNF α	No direct toxic effect
Secukinumab Package Insert	Secukinumab, 30 mg/kg single IV infusion	IL-17A	No dose-limiting toxicity
Taliercio M, Alessa D, Kessler DB	Secukinumab, 300 mg QD x 5 days	IL-17A	Dry, peeling skin; no other adverse effects
Alemtuzumab Package Insert	Alemtuzumab, 2 patients received 60 mg single IV infusion	CD52	Headache, rash, hypotension or sinus tachycardia
Belimumab Package Insert	Belimumab, 20 mg/kg IV infusion	BLyS (B-cell survival factor)	No increase in severity of adverse reactions compared with lower doses
Certolizumab Package Insert	Certolizumab, 800 mg SQ and 20 mg/kg IV	TNF α	No evidence of dose-limiting toxicity
Golimumab Package Insert	Golimumab, 5 patients received single IV infusion of up to 1000 mg	TNF α	No serious adverse reactions or other significant reactions
Omalizumab Package Insert	Omalizumab, single IV infusion of 4,000 mg	IgE	No evidence of dose-limiting toxicities

of infliximab and secukinumab during clinical trials with no dose-limiting adverse effects.^{6,7} An additional case of overdose of secukinumab with no resultant adverse effects has also been reported.⁸ The lack of dose-limiting toxicities in all of these instances highlights the generally well-tolerated nature of monoclonal antibodies as pharmacological agents. It is believed that this tolerance of high doses is due to the high specificity of therapeutic monoclonal antibodies, meaning that even at elevated doses, non-target cytokines or other proteins are not likely to be inhibited.⁹ At times,

higher doses may even have therapeutic benefits. For example, in a historic-prospective study of 147 patients treated with omalizumab in France, rates of drug discontinuation due to unsatisfactory therapeutic benefit were lower in those who overdosed on medication.¹⁰ In contrast to the relative safety of large doses of the aforementioned therapies, however, there are reports of adverse effects or significant laboratory abnormalities associated with overdose of other biologics. For instance, two patients with multiple sclerosis experienced headache, rash, hypotension,

and sinus tachycardia after an accidental single infusion of up to 60 mg of alemtuzumab.¹¹ Likewise, healthy volunteers who received 28 mg/kg single dose of tocilizumab all developed dose-limiting neutropenia.⁵ Contrary to trials for autoimmune and auto-inflammatory disorders, a study of 150 patients with New York Heart Association class III or IV heart failure treated with infliximab demonstrated adverse clinical outcome at 10mg/kg but not at 5mg/kg.¹²

Table 1 summarizes the aforementioned reports of administration of higher than standard doses of monoclonal antibodies.^{5-8, 11, 13-16} The discrepancy in effects of biologic overdose on patient safety emphasizes the importance of gathering more information specific to each agent in the setting of overdose. It appears as though the baseline health of the patient may play a role in their tolerance to higher dosages, as evidenced by the inconsistency of effect of infliximab dosage in healthy patients versus those with heart failure.^{6,12} However, there are currently too few reports in the literature to discern a pattern or ascertain if certain classes of biologic agents are more likely than others to lead to adverse events in the setting of overdose. Therefore, more information specific to each specific agent and biologic class is needed.

CONCLUSION

To our knowledge, we are the first to report a case of inadvertent overdose of ixekizumab. Like many reports of higher than recommended dosage of other monoclonal antibodies, our patient did not experience any adverse effects. We present this information in order for clinicians to be prepared to monitor and counsel their patients in the setting of inadvertent

overdose, as well as to highlight the need for careful and thorough dosing education when initiating patients on biologic therapies.

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References:

1. Refs Vecchio I, Tornali C, Bragazzi NL, Martini M. The Discovery of Insulin: An Important Milestone in the History of Medicine. *Frontiers in Endocrinology* 2018;9:613.
2. Kohler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature* 1975;256:495-7.
3. Kohler G, Milstein C. Derivation of specific antibody-producing tissue culture and tumor lines by cell fusion. *Eur J Immunol* 1976;6:511-9.
4. Emery P, Rondon J, Parrino J, Lin Y, Pena-Rossi C, Van Hoogstraten H, et al. Safety and tolerability of subcutaneous sarilumab and intravenous tocilizumab in patients with

- rheumatoid arthritis. *Rheumatology* (Oxford, England) 2019; 58(5):849-858.
5. Tocilizumab [package insert]. South San Francisco, CA: Genentech, Inc.; 2010.
 6. Infliximab [package insert]. Thousand Oaks, CA: Amgen, Inc.; 2019.
 7. Secukinumab [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015.
 8. Taliercio M, Alessa D, Kessler DB. Inadvertent Overdose of Secukinumab, Consequences, and Cautions. *Journal of Psoriasis and Psoriatic Arthritis* 2016; 1(4):147-9.
 9. Navarini AA, Muster MA, Kolios AG, Frische P, Glatz M, French LE, et al. Weight-Based Adaptation of TNF-Antagonist Induction versus Maintenance Dose. *Case Reports in Dermatology* 2011; 3(2):124-9.
 10. Molimard M, de Blay F, Didier A, Le Gros V. Effectiveness of omalizumab (Xolair) in the first patients treated in real-life practice in France. *Respiratory Medicine* 2008; 102(1):71-6.
 11. Alemtuzumab [package insert]. Cambridge, MA: Genzyme Corporation; 2001.
 12. Chung ES, Packer M, Hung Lo K, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation* 2003;107(25):3133-40.
 13. Belimumab [package insert]. Rockville, MA: Human Genome Sciences, Inc.; 2018.
 14. Certolizumab [package insert]. Smyrna, GA: UCB, Inc.; 2008.
 15. Golimumab [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2009.
 16. Omalizumab [package insert]. South San Francisco, CA: Genentech, Inc.; 2003.